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DGRD

0004/S020

17-Oct-1991

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FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC, INC. ATTN: TODD LANGEVIN 7000 CENTRAL AVE, NE. MINNEAPOLIS, MN 554323576	10/16/91	10/17/91	/ /
	DOCUMENT: PMA	CONTROL # P860004/S020 AMENDMENT	

SUBJECT:
SYNCROMED(R) INFUSION SYSTEM

	OFFICE	DATE REFERRED
3 COPIES OF VOLUME 1	CK	10/18/91
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ACM

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MEMO TO THE RECORD

DATE: 10/22/91

FROM: Chief, GHDB

DIVISION: DGRD

SUBJECT: Medtronic, Inc.
SYNCHROMED[R] INFUSION SYSTEM FOR THE INTRASPINAL ADMINISTRATION OF PRESERVATIVE-FREE MORPHINE SULFATE FOR THE TREATMENT OF CHRONIC INTRACTABLE PAIN OF NONMALIGNANT ORIGIN

This supplement has been submitted to FDA to request approval for the intraspinal (epidural and intrathecal) administration of preservative-free morphine sulfate sterile solution (10 mg/mL and 25 mg/mL) for the treatment of chronic intractable pain of nonmalignant origin via the SynchroMed[R] Infusion System. The System includes a programmable pump (Models 8611H, 8615), programmer (Model 8810), catheter access system (Model 8500-1), catheter (Model 8703), and accessories.

On October 16, 1991 CDRH issued an approvable letter for this supplement pending concurrence with a post-approval study to provide drug/device compatibility data for the life of the pump. previously been submitted for 25 and 50 mg/mL morphine sulfate

In this amendment the sponsor concurs with this post-approval requirement. In a phone conversation yesterday with Todd Langevin of Medtronic he confirmed that the additional compatibility studies will be performed using the same protocol as previous compatibility testing done by Medtronic. Therefore, I recommend approval.

Amalie C. Mattan

Amalie C. Mattan

P860004/S20A

Medtronic

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598
Telecopy: (612) 574-4879

RECEIVED
17 OCT 91 12 25
FDA/CDRH/OSE/DMC

16 October 1991

Center for Devices and Radiological Health
Food and Drug Administration
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850
Attention: Amalie Mattan

Re: P860004/20 SynchroMed Infusion System for Intraspinal Morphine Sulphate Administration

In the approvable letter issued 16 October 1991 CDRH requested a post approval study of the long term compatibility of preservative free morphine sulphate sterile solution with the SynchroMed pump as a condition for approval.

Medtronic hereby concurs with that condition and will submit annually the results of extended compatibility studies which simulate the expected duration of exposure.

If you have any questions, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

Todd Langevin
Product Regulation Manager

TL/jk

3

MP
DGRD
OH

P860004/S020

17-May-1993

mfc

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC, INC. ATTN: DAVID H. MUELLER 7000 CENTRAL AVE, NE. MINNEAPOLIS, MN 554323576	05/14/93	05/17/93	/ /
	DOCUMENT: PMA	CONTROL # P860004/S020 REPORT	

SUBJECT:
SYNCROMED(R) INFUSION SYSTEM

	OFFICE	DATE REFERRED
3 COPIES OF VOLUME 1	CK	5/17/93
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JML
&
TM

July 10, 1993

FROM: ADGD

SUBJECT: P860004/S20A
Dated: May 14, 1993
Received: May 17, 1993

TO: Record

This is a follow-up to a post-approval requirement for S20. The condition was to provide drug/pump compatibility information.

They report that the Elkins-Sinn morphine at 25mg/ml and 50mg/ml was initially found compatible for 16 weeks. **Check to see if this** [redacted] **the pump as well as the drug. The drug will be in**

[redacted]

They expanded the contact time up to [redacted] The materials were analyzed for effect at that point. The data indicate that the pump is unaffected.

Recommend

Discuss this with David Mueller at Medtronic. First, review our evaluation for S20 to get a sense of the rationale for the condition of approval and the data base on the 16 week exposure.

[redacted]

PARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
1390 Piccard Drive
Rockville, Maryland 20850

May 17, 1993

DAVID H. MUELLER
MEDTRONIC, INC.
7000 CENTRAL AVE, NE.
MINNEAPOLIS, MN 554323576

PMA Number: P860004
Letter Dated: 05/14/93
Received: 05/17/93
Product: SYNCROMED(R)
INFUSION SYSTEM

Dear MR. MUELLER:

The Center for Devices and Radiological Health (CDRH) acknowledges its receipt of the periodic report submitted by you for the premarket approval application (PMA) referenced above.

You will be notified of any need for additional information. Whenever additional information is requested by CDRH or voluntarily submitted by you, it shall be identified with the above PMA number, and the required number of copies shall be submitted as an amended report directly to:

Food and Drug Administration
Center for Devices and
Radiological Health
PMA Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

Questions concerning this submission may be directed to the PMA Staff at (301) 427-1186 or to the reviewing division within the CDRH Office of Device Evaluation.

Sincerely yours,

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Charles H. Kyper
Director, Premarket Approval Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

7

Medtronic

Medtronic Neurological
800 53rd Avenue NE
P.O. Box 1250
Minneapolis, MN 55440-9087
(612) 572-5000
1-800-328-0810
FAX: (612) 572-5078

May 14, 1993

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

RE: P860004/S20
Medtronic SynchroMed® Infusion System

Post-Approval Requirement

Long Term Compatibility of Preservative-free Morphine Sulfate Sterile Solution with the SynchroMed® pump

This submission provides the required annual post-approval requirement of extended material - drug compatibility studies. This requirement was agreed to by Medtronic in response to P860004/ S20 (approvable letter, response 16 October 1991.

This document contains confidential commercial and trade secret information and Medtronic respectfully request that it be given the maximum protection provided by law. Three copies of this document are provided as required by regulation.

Any question or comments, contact the undersigned at 612-572-5633.

Sincerely,

MEDTRONIC, INC., NEUROLOGICAL DIVISION

David H. Mueller
Regulatory Affairs Manager
DHM:dm

Attachments

P860004
Medtronic SynchroMed Infusion System

Post-Approval Requirement

Long Term Compatibility of Preservative-free Morphine Sulfate Sterile Solution with the SynchroMed® pump

This submission contains the Medtronic SynchroMed Infusion System Long Term Compatibility of Preservative-free Morphine Sulfate Sterile Solution with the SynchroMed® pump. This requirement was agreed to by Medtronic in response to P860004/ S20 (approvable letter, response 16 October 1991).

Elkins-Sinn preservative-free morphine formulated at 25 mg/ml and 50 mg/ml was originally found to be compatible with the SynchroMed System's infusion pathway for up to

The Medtronic SynchroMed Infusion System materials that come into contact with the drug solutions were incubated with

to see the effects of long term exposure of morphine on the materials. At the end of the incubation periods, the materials were analyzed for their physical properties. The analysis shows that all of the materials were within the specified values after the long term exposure.

The attached figures show the physical properties of the materials at The average standard deviation (std. dev.) is shown above the curves. All values obtained were within specification for each material. The concentration in all the samples

The weights of the material samples were within of the weight of the samples exposed to water for up to except for two samples; one sample at These samples were and than the water controls respectively.

None of the materials are affected by long term incubations (up to of the SynchroMed Infusion System's fluid pathway materials with high concentrations (25 and 50 mg/ml) of preservative free morphine sulfate.

Therefore, the Medtronic SynchroMed Infusion System's data demonstrates long term compatibility of preservative-free morphine sulfate sterile solution with the SynchroMed System's fluid pathway materials.

mp
DGRD

P8)04/S020

ACM
due 12/3

29-Aug-1991

FROM:	LETTER DATE	LOGIN DATE	DUE DATE
MEDTRONIC, INC. ATTN: TODD LANGEVIN 7000 CENTRAL AVE, NE. MINNEAPOLIS, MN 554323576	08/28/91	08/29/91	02/25/92
	DOCUMENT: PMA	CONTROL # P860004/S020	

SUBJECT:
SYNCROMED(R) INFUSION SYSTEM

	OFFICE	DATE REFERRED
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001

MEMO TO THE RECORD **DATE:** 10/08/91

FROM: Acting Chief, GHDB **DIVISION:** DGRD

SUBJECT: Medtronic, Inc.
SYNCHROMED[R] INFUSION SYSTEM FOR THE INTRASPINAL ADMINISTRATION OF PRESERVATIVE-FREE MORPHINE SULFATE FOR THE TREATMENT OF CHRONIC INTRACTABLE PAIN OF NONMALIGNANT ORIGIN

This supplement has been submitted to FDA to request approval for the intraspinal (epidural and intrathecal) administration of preservative-free morphine sulfate sterile solution (10 mg/mL and 25 mg/mL) for the treatment of chronic intractable pain of nonmalignant origin via the SynchroMed[R] Infusion System. The System includes a programmable pump (Models 8611H, 8615), programmer (Model 8810), catheter access system (Model 8500-1), catheter (Model 8703), and accessories.

PERTINENT BACKGROUND

- On March 14, 1988 the SynchroMed[R] Infusion System for the intravascular delivery of the chemotherapy agents floxuridine and doxorubicin was approved by CDRH. Subsequent approvals have been granted for the intravascular delivery of cisplatinum, methotrexate, heparin, and clindamycin.

- On January 30, 1991 CDRH issued an approvable letter for the SynchroMed[R] Infusion System for the intrathecal administration of the antispasticity drug baclofen (Lioresal[R]), subject to the approval of the Lioresal[R] NDA by CDER.

- On March 11, 1991 The SynchroMed[R] Infusion System was approved by CDRH for the epidural infusion of preservative-free morphine sulfate for the treatment of chronic intractable pain of malignant origin.

- On July 19, 1991 Infumorph[TM] 200 and 500 CII (preservative-free morphine sulfate sterile solution) was approved by CDER for use in continuous microinfusion devices for intrathecal or epidural infusion in the treatment of intractable chronic pain.

- On July 25, 1991 the Synchromed[R] Infusion System was approved by CDRH for the intrathecal administration of preservative-free morphine sulfate for the treatment of chronic intractable pain of

malignant origin.

Medtronic is now seeking approval to expand the indications of the pump to deliver Infumorph for pain of nonmalignant origin. (Note that the origin of pain is not specified in the approved drug labeling.)

INFUMORPH APPROVAL

The drug is approved for use in continuous microinfusion devices. Implantable pumps are addressed in the following portions from the Dosage and Administration section of the labeling:

> "CANDIDATES FOR NEURAXIAL ADMINISTRATION OF INFUMORPH™ IN A CONTINUOUS MICROINFUSION DEVICE SHOULD BE HOSPITALIZED TO PROVIDE ADEQUATE PATIENT MONITORING DURING ASSESSMENT OF RESPONSE TO SINGLE DOSES OF INTRATHECAL OR EPIDURAL MORPHINE. HOSPITALIZATION SHOULD BE MAINTAINED FOR SEVERAL DAYS AFTER SURGERY INVOLVING THE INFUSION DEVICE FOR ADDITIONAL MONITORING AND ADJUSTMENT OF DAILY DOSAGE."
>
> "Familiarization with the continuous microinfusion device is essential. The desired amount of morphine should be withdrawn from the ampul through a microfilter. **To minimize risk from glass or other particles, the product must be filtered through a 5 μ (or smaller) microfilter before injecting into the microinfusion device."**
>
> "Intrathecal dosage: The starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose intrathecal bolus injections of regular DURAMORPH® 0.5 mg/mL or 1 mg/mL, with close observation of the analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device."
>
> "Epidural dosage: The starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural bolus injections of regular DURAMORPH® (Morphine Sulfate Injection USP) 0.5 mg/mL or 1 mg/mL, with dose observation for analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device."

GENERAL HOSPITAL BRANCH POLICY AND GUIDANCE

The policy regarding the approval of implantable infusion pumps and the addition of a drug for an already approved implantable infusion pump was outlined at a March 5, 1991 meeting of the General Hospital Devices Advisory Panel at which two implantable infusion pumps were reviewed. The General Hospital Branch Chief made a statement to the Panel at the

beginning of each session. Hard copies of these statements were then distributed to manufacturers in attendance.

The policy and guidance can best be summarized by the following excerpts from those statements to the Panel:

> "You [the GH Panel] are asked to decide whether the premarket approval applications ...PMAs... for the infusion pumps you will consider today provide reasonable assurance that the devices are safe and effective for their intended use. The intended use of an infusion pump, simply stated, is to deliver an approved drug for the intended use, by the route of administration, and the dosage defined in the approved drug labeling. We are NOT here today to determine the safety and effectiveness of any drug. The safety and effectiveness of the drugs encountered today have been, or soon will be, established.
>
> "How do drugs mesh with pumps in a regulatory sense? FDA approvals for <u>most</u> EXTERNAL infusion pumps are independent of specific drugs. <u>Some</u> external pumps are dedicated to a specific drug. On the other hand, specific drugs and the drug labeling must <u>always</u> be considered for implantables. Still, even with implantables there is flexibility. Generally, once an implantable pump is clinically qualified for a particular route of administration, additional drugs for the same route of administration can be added to the pump labeling without clinical data. Manufacturers must submit drug and device stability and compatibility data and the labeling for the drug and device must otherwise be compatible. In essence, one does not have to reprove the fundamental safety and effectiveness of the pump."
>
> ...
>
> "To reiterate, the implantable infusion pump is intended simply to infuse a drug. It is the drug labeling that defines the use of the drug. The pump must be capable of providing the drug as the drug labeling directs. We are NOT here to determine the safety and effectiveness of any drug."

At the time of the March 5, 1991 General Hospital Advisory Panel Meeting the exact indications for the Infumorph were not totally clear to CDRH. It was anticipated that Infumorph would be indicated for treatment of chronic intractable pain. Since the Panel had only previously dealt with implantable pumps for infusion of drugs for the treatment of chronic intractable pain of malignant origin, they were instructed by FDA to consider the possibility of the nonspecific drug labeling regarding the origin of the pain. The Panel was asked by the General Hospital Branch Chief to consider the following issue:

"What are the implications of the drug indication, as defined, for the device? Long-term reliability for treatment of chronic benign pain must be considered. This was less of a concern from a risk/benefit angle for malignant pain."

The Panel responded to this issue by recommending that 50 patients be followed for 24 months to demonstrate the safety and effectiveness of an implantable infusion system for chronic intraspinal drug administration. The Panel indicated that the focus of the data over that 24 month period be on device complications.

REVIEW

Since the fundamental safety and effectiveness of the SynchroMed^{R} Infusion System has been established, the following are necessary to expand the indications to chronic intractable pain (malignant or benign origin):

1. evidence that the device is clinically qualified for the intraspinal route of administration;

2. drug stability data for the period of time it may be stored in the pump reservoir;

3. drug/device compatibility data for the life of the pump;

4. data demonstrating the safety and effectiveness of chronic intraspinal drug administration; and

5. revised labeling.

The five above issues have been addressed as follows:

1. The device has been approved by CDRH for epidural and intrathecal delivery of morphine sulfate for the treatment of chronic intractable pain of malignant origin. Thus, the sponsor has demonstrated that the device is clinically qualified for the intraspinal route of administration.

2. Stability data were submitted as part of the supporting information for number one above.

3. Compatibility data were submitted for 25 and 50 mg/mL morphine sulfate for [redacted] as part of the supporting information for number one above. [redacted] The expected life of the pump is approximately 4 years, so [redacted]

compatibility data for at least 4 years is required. As was communicated to other implantable pump manufacturers, these data may be collected in a post-approval study using Infumorph.

4. As recommended by the Panel, data from a study involving 50 patients followed for 24 months which demonstrate the safety and effectiveness of an implantable infusion system for intraspinal drug administration are necessary to show long-term reliability. The Panel also indicated that the focus of these data be on device complications. Medtronic has submitted data from their intrathecal baclofen study in support of this requirement. (As stated above, approval of the SynchroMed^{R} Infusion System for intrathecal baclofen is pending approval of the drug by CDER.)

The baclofen data have been collected under several IDE/IND protocols, and have previously been reviewed under a separate PMA supplement. The length of follow-up is summarized in the following table:

FACTOR	12 - 24 MONTHS	≥ 24 MONTHS	TOTAL
N	69	52	121
Age (years)	36.4 ± 1.6	40.1 ± 1.8	38.0 ± 1.2
Males	46	29	75
Females	23	23	46
Follow-up (months)			
Mean ± SE	16.7 ± 0.4	42.0 ± 2.4	27.6 ± 1.5
Median	17.0	36.0	21.0
Range	12 - 23	24 - 81	12 - 81

These data more than adequately meet the time requirements recommended by the Panel, as 52 patients have been followed for greater than 24 months, with both mean and median follow-up greater than 24 months.

Complications for all US studies are reported. System complications are broken down into: pump (stall, catheter port occlusion, underinfusion), catheter (angulation/kink, occlusion, break, dislodgement), access port (connector kink), programmer, and pocket (infection, hygroma). Procedural complications are broken down into: reservoir contamination, catheter dislodgment, CSF leak/headache, catheter disconnection, catheter lacerated, pocket infection/erosion/revision, programming error, meningitis, catheter reposition, refill error, seroma/hematoma, catheter angulation, catheter puncture, catheter break (prior to implant), subcutaneous catheter fragment, wound dehiscence, pump site

discomfort, pump inverted at implant, catheter repositioned, and back incision infection. The complications and complication rates reported are not unusual for this type of device and its components.

These data demonstrate the safety and effectiveness of chronic intraspinal drug administration via the SynchroMed^{R} Infusion System.

5. Medtronic has submitted adequate revised labeling. The previous labeling for intraspinal delivery of morphine sulfate specified pain of malignant origin. The revised labeling indicates the device for the treatment of chronic intractable pain. The implantation and refill procedures remain the same.

In summary, the file is deficient in one area: compatibility. This deficiency can be handled in a post-approval study. Therefore, I recommend an approvable letter be issued at this time, and approval be granted after the sponsor has agreed to the post-approval requirements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
1390 Piccard Drive
Rockville, Maryland 20850

August 29, 1991

TODD LANGEVIN
MEDTRONIC, INC.
7000 CENTRAL AVE, NE.
MINNEAPOLIS, MN 554323576

PMA Number: P860004 SUP 020
Letter Dated: 08/28/91
Received: 08/29/91
Product: SYNCROMED(R)
INFUSION SYSTEM

-- Dear MR. LANGEVIN:

The Center for Devices and Radiological Health (CDRH) acknowledges its receipt of the premarket approval application (PMA) supplement submitted by you for the above referenced device. This PMA supplement has been assigned an unique document control number. Failure to reference this supplement number in further correspondence may result in processing delays. All further correspondence shall be referred to as amendments to the PMA supplement, and the required number of copies bearing the above PMA supplement number shall be submitted directly to:

Food and Drug Administration
Center for Devices and
Radiological Health
PMA Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, Maryland 20850

You will be notified of any need for additional information and the CDRH filing decision. Questions concerning this submission may be directed to the PMA Staff at (301) 427-1186 or to the reviewing division within the CDRH Office of Device Evaluation.

Sincerely yours,

/S/

Charles H. Kyper
Director, Premarket Approval Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

008

Medtronic

P860004/S20C2V1

Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598

PMA P860004/S1, Amendment 8

28 August 1991

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

Re: Amendment 8 to PMA Supplement P860004/S1
SynchroMed® Infusion System for the administration of preservative-free morphine sulfate for the treatment of chronic intractable pain of nonmalignant origin

Medtronic hereby submits amendment 8 to PMA P860004/S1 for the SynchroMed® Infusion System which requests approval for the administration of preservative-free morphine sulfate for the treatment of chronic intractable pain of nonmalignant origin.

This submission contains confidential trade information. Medtronic requests that it be given full protection under the law. Three copies of this report are provided per regulation.

Sincerely yours,
Medtronic, Inc.

Todd Langevin
Product Regulation Manager

009

PMA P860004/S1, Amendment 8

Medtronic SynchroMed® Infusion System for the Administration of Preservative-Free Morphine Sulfate Solution for the Treatment of Chronic Intractable Pain of Nonmalignant Origin

SUBMITTED 28 AUGUST 1991

TABLE OF CONTENTS

List of Appendices

I. INTRODUCTION

A. Background

Following FDA approval on 19 July 1991, of Infumorph™ 200 and Infumorph™ 500 (Elkins-Sinn, Inc, Cherry Hill, NJ) preservative-free morphine sulfate solutions, the Medtronic SynchroMed Infusion System was approved on 25 July 1991, by the Center for Devices and Radiological Health of FDA for the intrathecal infusion of morphine sulfate for treatment of chronic intractable pain of malignant origin. The SynchroMed Infusion System had been previously approved for epidural administration of morphine sulfate for treatment of chronic intractable pain of malignant origin based on clinical data from the intrathecal route of administration.

Infumorph™ 200 and Infumorph™ 500, developed for use in continuous microinfusion devices, are indicated for intrathecal or epidural infusion in the treatment of intractable chronic pain. The pain etiology is not stipulated. (See Appendix 1 for Infumorph package insert).

Though approved for the treatment of chronic pain of malignant origin and a suitable drug is commercially available, the SynchroMed Infusion System was not approved for the treatment of chronic pain of nonmalignant origin. While stability and compatibility of preservative-free morphine sulfate with the SynchroMed System components under conditions of use had been demonstrated and served, in part, as the basis for approval for pain of malignant origin, FDA determined that evidence of safety and effectiveness had not been demonstrated for the treatment of chronic pain of nonmalignant origin. Specifically, documentation of long-term performance and reliability of the pump and catheter had not been presented.

On 5 March 1991, the Advisory Panel of the General Hospital and Personal Use Device Section of the General Medical Devices Branch recommended that 43 patients each be followed for 24 months to demonstrate the safety and effectiveness of an implantable infusion system for the chronic intraspinal delivery of drugs.The panel also recommended that the focus of the data over that 24-month period be on device complications.

One Place Your Text Could Go (See Documentation Section 6)

In fulfillment of this requirement, Medtronic submits data which has been obtained from studies conducted under IDE G820002 of the SynchroMed Infusion System for the intrathecal administration of baclofen to treat chronic intractable spasticity. Like patients with chronic pain of nonmalignant origin, spasticity patients require treatment for extended periods. The route of administration is the same. Preservative-free morphine sulfate solution and baclofen solution are both administered to the intrathecal space. Both therapies use Model 8611H SynchroMed pump, the Model 8703 Spinal Catheter and the 8810 SynchroMed Programmer. The implantation procedure for both therapies are identical.

On 5 March 1991, in remarks to the General Hospital and Personal Use Device Section of the General Medical Devices Branch Advisory Panel (Appendix 2), Mr. Timothy A. Ulatowski, Chief, General Hospital Devices Branch, stated, "Generally, once an implantable pump is clinically qualified for a particular route of administration, additional drugs for the same route of administration can be added to pump labeling without clinical data." On 30 January 1991, FDA issued an approvable letter to Medtronic for the SynchroMed Infusion System for the intrathecal administration of baclofen solution pending notification to CDRH that intrathecal baclofen had been approved by CDER. This is an indication by CDRH that the SynchroMed Infusion System has been clinically qualified for the intrathecal route of administration. The actual approval is contingent on drug approval. The clinical data on which the approvable letter was based was subsequently updated through 1 April 1991 and submitted to CDRH on 22 August 1991. Medtronic believes that this clinical data demonstrates the safety and effectiveness of the SynchroMed Infusion System when used for the chronic delivery of intraspinal medications.

It is on this basis that Medtronic requests CDRH to consider the data collected from intrathecal baclofen studies from July 1984 through April 1991, in support of approval of the SynchroMed Infusion System for the administration of preservative-free morphine sulfate solution for the treatment of chronic intractable pain of nonmalignant origin.

B. Organization of Clinical Data

The data contained in this amendment have been organized to provide evidence of chronic safety and effectiveness of the SynchroMed Infusion System for intraspinal drug delivery. Several baclofen studies have been conducted in the U.S. and Europe. These studies are described later in this report. All patients who have been followed for greater than 12 months in U.S. studies have been selected and evaluated as a cohort. The data from these patients are summarized in the chronic clinical data summary and serve to satisfy the requirements for patient numbers, length of follow-up and elements of data collection stipulated by the General Hospital and Personal Use Device Section of the General Medical Devices Advisory Panel.

For reference, data from all patients followed in the U.S. and in Europe are also provided in the comprehensive clinical data summary.

II. CHRONIC CLINICAL DATA SUMMARY

A. Description of Patient Population

As of 1 April 1991, a total of 121 patients from eight U.S. clinical studies have been followed for 12 months or longer. Mean follow-up for these patients is 27.6 ± 1.5 months and a median of 21 months (range: 12 - 81 months). Of these, 52 patients have follow-up of greater than 24 months, with a mean of 42 ± 2.4 months and a median of 36 months.

Table 1. Summary of Patient Population - All Patients Followed ≥ 12 Months

Factor	12 - 24 months	≥ 24 months	Total
N	69	52	121
Age (yrs)	36.4 ± 1.6	40.1 ± 1.8	38.0 ± 1.2
Males	46	29	75
Females	23	23	46
Follow-up (mos)			
Mean ± SE	16.7 ± 0.4	42.0 ± 2.4	27.6 ± 1.5
Median	17.0	36.0	21.0
Range	12 - 23	24 - 81	12 - 81

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While the IND sponsor may vary, each of the eight U.S. clinical studies have been conducted under Medtronic's IDE G820002. A listing of each study is shown below.

1. Protocol
2. Protocol
3. Protocol
4. Protocol
5. Protocol
6. Protocol
7. Protocol
8. Protocol

Though valid information, European data is not relied on to demonstrate chronic safety and effectiveness but used rather as supporting information. The SynchroMed Infusion System is commercially available in Europe and may be freely purchased by physicians. Medtronic is conducting market surveillance activities to collect information on system performance.

Patients from U.S. studies selected for follow-up of greater than 12 months as of 1 April 1991, are shown in Table 2.

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Table 2. Patient Demograhics

Patient ID	Protocol Number	Age/Sex	Implant Date	Months Follow-up	Status* (1 Apr '91)
		42/F	Jul 84	80	A
		19/	Jul 84	81	A
		53/	Jul 84	80	A
		35/	Sep 84	79	A
		39/	Oct 84	78	A
		22/	Dec 84	76	A
		55/	Jul 85	68	A
		40/	Dec 85	63	A
		53/	Apr 86	59	A
		60/	Jul 86	56	A
		39/	Jan 87	49	A
		40/	Jan 87	50	A
		44/	Feb 87	50	A
		42/	Mar 86	48	A
		25/	Mar 87	49	A
		36/	Apr 87	48	A
		10/	Jun 87	45	A
		41/	Jun 87	44	A
		37/	Jul 87	44	A
		45/	Aug 87	43	A
		49/	Sep 87	29	D
		42/	Oct 87	40	A
		40/	Oct 87	42	A
		48/	Nov 87	40	A
		22/	Dec 87	35	A
		59/	Jan 88	34	A
		29/	Jan 88	38	A
		31/	Feb 88	36	A
		36/	Jan 88	32	A
		42/	Apr 88	28	A
		45/	May 88	35	A

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Patient ID	Protocol Number	Age/Sex	Implant Date	Months Follow-up	Status* (1 Apr '91)
		30/	May 88	35	A
		56/	Jun 88	34	A
		24/	Apr 89	22	A
		36/	Feb 90	13	A
		47/	Mar 90	13	A
		23/	Apr 89	23	A
		34/	May 89	21	A
		22/	Sep 89	18	A
		25/	Dec 89	14	A
		25/	Jan 90	15	A
		41/	Feb 90	14	A
		39/	Feb 90	12	A
		40/	Aug 89	21	A
		32/	Dec 89	14	A
		37/	Jul 89	20	A
		39/	Mar 90	13	A
		49/	Feb 90	14	A
		29/	Nov 88	26	A
		42/	Jan 89	24	A
		41/	Apr 89	20	A
		37/	Apr 89	21	A
		31/	May 89	22	A
		33/	Jul 89	18	A
		44/	Aug 89	16	A
		33/	Nov 89	17	A
		30/	Jan 90	13	A
		54/	Oct 88	30	A
		36/	Jun 89	22	A
		25/	Jan 90	15	A
		45/	Feb 90	14	A
		31/	Mar 90	13	A
		62/	Jan 90	14	A
		48/	Apr 90	12	A

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Patient ID	Protocol Number	Age/Sex	Implant Date	Months Follow-up	Status* (1 Apr '91)
		27/	Jan 89	27	A
		52/	Sep 89	25	A
		44/	Aug 89	19	A
		41/	Mar 89	18	A
		65/	Mar 89	12	A
		37/	Dec 89	16	A
		40/	Nov 88	18	A
		50/	Dec 88	27	A
		36/	Feb 89	26	A
		43/	Jun 89	20	A
		28/	Jun 89	19	A
		30/	Oct 89	18	A
		39/	Oct 89	16	A
		41/	Oct 89	16	A
		43/	Mar 90	13	A
		52/	Sep 89	17	A
		27/	Sep 89	17	A
		55/	Mar 90	12	A
		35/	Jan 90	12	A
		54/	May 88	34	A
		57/	Dec 88	22	A
		25/	Nov 88	28	A
		60/	Nov 88	28	A
		71/	Apr 89	24	A
		46/	Apr 89	23	A
		18/	Jul 89	21	A
		48/	Aug 89	19	A
		41/	Aug 89	18	A
		39/	Aug 89	19	A
		40/	Aug 89	20	A
		39/	Oct 89	15	A
		50/	Oct 89	17	A
		56/	Oct 89	17	A
		18/	Nov 89	13	A

Patient ID	Protocol Number	Age/Sex	Implant Date	Months Follow-up	Status* (1 Apr '91)
		66/	Nov 89	17	A
		20/	Dec 89	16	A
		58/	Jan 90	13	A
		21/	Jan 90	14	A
		35/	Apr 90	12	A
		32/	Feb 88	36	A
		44/	Feb 88	37	A
		59/	Mar 88	34	A
		39/	Oct 88	29	A
		40/	Mar 89	24	A
		18/	Aug 89	19	A
		21/	Mar 89	25	A
		53/	Sep 89	16	A
		28/	Jan 90	13	A
		36	Jan 90	14	A
		26/	Feb 89	27	A
		18/	Jun 89	23	A
		18/	Oct 89	19	A
		8/	Nov 89	14	T
		26	Nov 89	14	T
		9/	Jul 89	19	T
		20	Feb 89	27	A
		14	Aug 89	21	A

* A = patient still active in study
T = patient terminated from study; termination was not related to device
D = patient died from disease

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B. Device Related Complications

Device related complications for all U.S. patients followed for greater than 12 months are listed in Table 3. Complications are divided according to those directly related to procedural events and those directly attributable to device design or manufacture. Complications that occurred in patients implanted with a prototype device are indicated.

Table 4 is a similar table for patients followed 24 months or greater.

Table 3. Summary of Device Related Complications - All Patients Followed ≥ 12 Months

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	15	
Catheter Break	5	
Catheter Occlusion	5	
Catheter Dislodgement	4	
Pump Stall	3	
Overinfusion	2	
Catheter Disconnect	1	
Port Connector Kink	1	
Underinfusion	1	
Intermittent Alarm	1	
Total	38	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Reservoir Contamination	23	
Catheter Dislodgement	7	
Pocket Infection/Erosion/ Revision	5	
Catheter Disconnection	4	
Catheter Lacerated	4	

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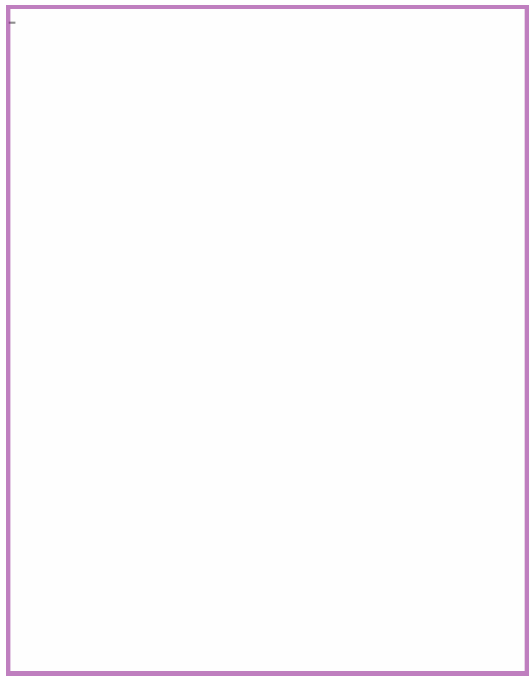
Catheter Angulation	3
CSF Leak	2
Refill Error	2
Catheter Puncture	2
Catheter Repositioned	2
Seroma/Hematoma	2
Catheter Break at implant	1
Removal of Subcut. Cath. Fragement	1
Wound Dehiscence	1
Programming Error	1
Meningitis	1
Total	61
Grand Total	99



[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.
[c] Prototype design manufactured prior to October, 1985.
[d] Reservoirs treated with gentamicin, pumps not replaced.

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Table 4. Summary of Device Related Complications - All Patients Followed ≥ 24 Months

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	14	
Catheter Break	3	
Catheter Occlusion	3	
Catheter Dislodgement	2	
Pump Stall	2	
Overinfusion	2	
Port Connector Kink	1	
Intermittent Alarm	1	
Total	28	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Reservoir Contamination	22	
Catheter Dislodgement	5	
Pocket Infection/Erosion/ Revision	2	
Catheter Disconnection	4	
Catheter Lacerated	2	

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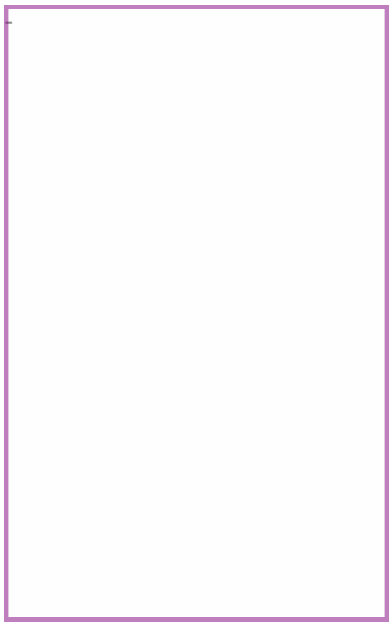
Catheter Angulation	2
CSF Leak	1
Refill Error	1
Catheter Puncture	1
Catheter Repositioned	1
Seroma/Hematoma	1
Catheter Break at implant	1
Removal of Subcut. Cath. Fragement	1
Wound Dehiscence	1
Programming Error	1
Total	44
Grand Total	72



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[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.
[c] Prototype design manufactured prior to October, 1985.
[d] Reservoirs treated with gentamicin, pumps not replaced.

System complications for various components of the SynchroMed Infusion System are summarized in Table 5 for all patients followed greater than 12 months. The most common system complication type was that related to the catheter. These occurred at a rate of about 19.6%. Of the 112 patients implanted with the current system design, 22 experienced at least one system complication during the course of their therapy. Mean follow-up for the 112 evaluable patients is 23 months.

Table 5. Distribution of Complications By System Component - All Patients Followed ≥ 12 Months

	N	%
Patients Implanted	121	NA
Patients Implanted With Pump/Catheter Prototype	9	NA
Patients Evaluated	112	100
Patients Reporting System Complications	22	19.6
Total System Complications	26	23.2
System Component		
Pump	3	2.7
Catheter	22	19.6
Access Port	1	0.9
Programmer	0	0
Pocket	0	0
Total	26	23.2

Complications are further described in Table 6 according to type of catheter complication and type of pump complication.

Table 6. Distribution of System Complications - All Patients Followed ≥ 12 Months

	N	%
Number of Patients Followed ≥ 12 months	121	NA
Number Implanted With Pump/Catheter Prototype	9	NA
Number of Patients Evaluated	112	100
Complication Description		
Catheter Angulation	7	6.2
Catheter Occlusion	5	4.5
Catheter Break	5	4.5
Catheter Dislodgement	4	3.6
Pump Stall	2	1.8
Pump Underinfusion	1	0.9
Port Connector Kink	1	0.9
Catheter Disconnect	1	0.9
Total	26	23.2

The most common system complications observed have been those related to catheter performance. A retrospective comparison was made of Medtronic Model 8703 Spinal Catheter implanted in patients with follow-up of ≥ 12 months to other commercially available spinal catheters. Information for commercially available catheters was obtained from the scientific literature. A complete reference listing is provided in Appendix 3.

On a per catheter basis, complications were slightly higher for Model 8703 compared to commercial catheters. However, If one is assessing the chronic performance of a spinal catheter, it is important to consider months of experience to understand what happens over the implant life of the catheter. Total months follow-up for Model 8703 is nearly double that of the commercial catheters evaluated, while the number of Model 8703 catheters evaluated is less than one-third. Complications per month for Model 8703 is 0.8% versus 3.4% for

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commercially available catheters. In this retrospective analysis, over time, the Model 8703 catheter is superior to commercially available catheters.

Table 7. Comparison of Spinal Catheter Performance

	Model 8703	Commercial[a]	
Total Catheters Evaluated	112	383	
Total Months Experience	2590	1379	
Complication Type			
Catheter Kink	7	17	
Catheter Occlusion	5	17	
Catheter Break/Leak	5	5	
Catheter Dislodgement	4	0	
Catheter Disconnect	1	0	
Hygroma	0	8	
Total	22	47	
Complications per Catheter	19.6%	12.3%	p = 0.05
Complications per Month	0.8%	3.4%	p < 0.001

[a] Literature References

Auld AW; Spine, 1985
Plummer JL; Pain, 1991
Shetter AG; J Neurosurg, 1982
Onofrio BM; Mayo Clin Proc, 1981
Krames ES; Cancer, 1985
Greenberg HS; J Neurosurg, 1982
Coombs DW; Can Anesth Soc, 1983
Woods WA; Anesth, 1982
Penn RD; J Neurosurg, 1987
Leavens ME; J Neurosurg, 1982
Harbaugh RE; J Neurosurg, 1982
Delhaas EM; Lancet, 1984
Cobb CA; Surg Neurol, 1984

C. Summary

Medtronic requests approval of the SynchroMed Infusion System for the treatment of pain of nonmalignant origin. To demonstrate the safety and effectiveness of the System for chronic intraspinal infusion of medications, Medtronic has presented clinical data for 121 patients followed for ≥ 12 months. The data fulfills the requirements set forth by the General Hospital and Personal Use Device Section of the General Medical Devices Branch Advisory Panel who stipulated that to demonstrate the safety and effectiveness of an implantable infusion system for the chronic intraspinal delivery of drugs, 43 patients each must be followed for at least 24 months. Medtronic has presented data from 52 such patients.

The baclofen clinical data is considered by Medtronic to be valid and adequate to support this approval because of the common route of drug delivery and the similarity of spasticity management and management of pain of nonmalignant origin using an implantable infusion system. Both therapies use the SynchroMed Model 8611H pump and Model 8703 catheter, which are implanted using the same surgical procedure. Baclofen solution and preservative-free morphine sulfate solution are each delivered by the intrathecal route of administration for long durations. The SynchroMed Infusion System was determined approvable by CDRH of FDA for the intrathecal administration of baclofen to treat chronic spasticity. This suggests that the SynchroMed is clinically qualified for the intrathecal route of administration.

Medtronic considers the clinical data collected for the SynchroMed Infusion System when used for the delivery of intrathecal baclofen to be valid scientific data which support the safety and effectiveness of the device when used to deliver intrathecal preservative-free morphine sulfate solution for the treatment of chronic pain of nonmalignant origin. The data presented adequately demonstrate the safety of the device and the absence of unreasonable risk when used under the conditions of intended use and in accordance with the final labeling. Refer to Appendix 4 for SynchroMed draft labeling.

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III. Comprehensive Clinical Data Summary

A. Description of Studies

The following section summarizes clinical experience for all patients enrolled in intrathecal baclofen clinical studies who were implanted with the SynchroMed Infusion System through 1 April 1991. This information was reported to CDRH on 22 August 1991 as a clinical data update of PMA P860004/S11, SynchroMed Infusion System for the Administration of Intrathecal Baclofen.

The U.S. clinical studies are comprised of the eight studies listed earlier.

The European studies are comprised of two studies conducted in Europe. for which Medtronic is conducting safety surveillance activities. Medtronic was provided limited access to the data. These studies are:

1. Protocol [redacted] multicenter
2. Protocol [redacted] multicenter

An overview of each study is given including patient demograhic information and characteristics of the patients.

Table 8 summarizes the clinical studies groupings contained in this report.

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Table 8. Summary Table of Clinical Studies

Study Groupings	Number Screened	Number Implanted	IND Sponsor	IND Number
U.S. Monitored Studies				
Protocol	20	20	Penn/ Medtronic	22,747
Protocol	34[a]	32[a]	Penn/ Medtronic	22,747
Protocol	93	75	Medtronic	30,648
Protocol	66	61	Medtronic	30,648T
Protocol	32	28	Penn/ Medtronic	22,747
Protocol	16	16	Loubser	25,969
Protoco	3	2	Penn	22,747
Protocol	36	18	Albright	31,920
European Studies				
Protocol	28	28	NA	NA
Protocol	166	164	NA	NA

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[a] Total is inclusive of the patients from Protocol I

U.S. Monitored Studies

1. PROTOCOL I - A DOUBLE-BLIND, RANDOMIZED CROSS-OVER STUDY OF INTRATHECAL BACLOFEN VERSUS PLACEBO

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity caused by spinal cord lesions or multiple sclerosis in a randomized, double-blind, cross-over study.

Study Population

Twenty adults suffering from severe chronic spasticity due to spinal cord injury (N = 10) or multiple sclerosis (N = 10) were enrolled. The patients had stable spasticity refractory to oral baclofen or the side effects from oral baclofen were unacceptable at effective doses. The patients exhibited adequate CSF flow and must have voluntarily signed informed consent. Prior to pump implantation, patients responded to ≤ 100 µg single bolus dose of intrathecal baclofen. Following pump implantation, patients were randomized to receive either baclofen or placebo for a period of three days. Safety and efficacy assessments were performed throughout. The pump was then emptied and filled with the alternate drug which was also administered for three days.

Table 9 summarizes patients for this study. As these patients were enrolled in Protocol following completion of this study, demographic information is included with the demographics of Protocol (Table 11).

Table 9. Protocol I - Summary of Patient Characteristics

Factor	MS	SCI	Total
N	10	10	20
Mean Age (years)	40.0	35.1	37.6
Sex:			
Males	3	8	11
Females	7	2	9
Mean Duration of Spasticity (years)	4.4	1.6	3.0

Study Status

This study was initiated on 7 July 1986 and completed on 5 May 1988.

2. PROTOCOL [redacted] OPEN LABEL , LONG-TERM SAFETY AND EFFICACY TRIAL OF INTRATHECAL BACLOFEN IN PATIENTS WITH SEVERE SPASTICITY [redacted]

Objective

To evaluate the long-term safety and efficacy of chronic intrathecal baclofen administered via implantable drug pump in the treatment of severe spasticity caused by spinal cord lesions or multiple sclerosis in a randomized, double-blind, cross-over study.

Study Population

Patients suffering from severe chronic spasticity due to spinal cord injury or multiple sclerosis were enrolled in the trial. Thirty-four patients were screened, 32 were implanted with a pump and are evaluable. The patients had stable spasticity refractory to oral baclofen or the side effects from oral baclofen were unacceptable at effective doses. The patients had adequate CSF flow, voluntarily

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signed informed consent and, prior to pump implantation, responded to ≤ 100 µg single bolus dose of intrathecal baclofen. Twenty of these patients also participated in Protocol I described above. Table 10 summarizes patient characteristics for these patients. Table 11 shows patient demographics.

[redacted] Summary of Patient Characteristics

Factor	
Total Patients	34
Mean Age (years)	40
Sex:	
Males	17
Females	17
Duration of Spasticity (years)	3.0 (0.3-41.4)
Diagnosis	
SCI	16
MS	16
Other	2
Follow-up	
Median	48.6
Mean	49.5
Range	5.4-81.1

Following screening and pump implant, patients returned monthly for reservoir refills and evaluation of safety and efficacy.

Study Status

This study was initiated on 14 June 1984. Enrollment is complete. Long-term follow-up will continues. All patients currently active will be "rolled over" to [redacted] which is the [redacted] IDE following completion of required follow-up and IRB approval.

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TABLE 11. PROTOCOL IB. PATIENT DEMOGRAPHICS							
Pt. ID	Primary Dx(a)	Site of Injury(b)	Age/Sex	Duration Spasticity (yrs)	Implant Date(c)	Months Follow-up(d)	Status(e)
[redacted]	SCI	T4	42/[redacted]	2.0	[redacted]-Jul-84	80.0	A
	SCI	T4	19/	3.0	-Jul-84	81.1	A
	MS	NA	53/	19.0	-Jul-84	80.3	A
	MS	NA	35/	8.0	Sep-84	78.8	A
	MS	NA	39/	20.0	Oct-84	77.5	A
	SCI	C6	22/	20.0	Dec-84	75.7	A
	SCI	C7	55/	24.0	-Jul-85	68.3	A
	SCI	T5	40/	0.8	Dec-85	62.7	A
	MS	NA	53/	3.0	Apr-86	59.2	A
	MS	NA	60/	3.0	-Jul-86	55.5	A
	MS	NA	39/	1.0	Jan-87	49.1	A
	MS	NA	40/	1.0	Jan-87	50.2	A
	MS	NA	44/	2.0	Feb-87	49.6	A
	SCI	T12	42/	0.6	Mar-87	48.5	A
	SCI	T9	25/	0.4	Mar-87	48.6	A
	SCI	T6-8	36/	2.5	Apr-87	47.6	A
	SCI	C1	10/	2.1	Jun-87	45.1	A
	SCI	C7	41/	0.6	Jun-87	44.4	A
	SCI	C5	37/	2.0	-Jul-87	43.9	A
	SCI	C5	45/	5.0	Aug-87	42.9	A
	SCI	T4-5	49/	1.0	Sep-87	29.2	D
	MS	NA	42/	2.0	-Oct-87	40.3	A
	MS	NA	40/	1.0	-Oct-87	42.2	A
	MS	NA	66/	ND	T IMPL	ND	Sc
	MS	NA	48/	0.6	Nov-87	40.1	A
	MS	NA	48/	ND	T IMPL	ND	Sc
	SCI	T6	22/	1.1	Dec-87	34.9	A
	MS	NA	59/	19.0	-Jan-88	34.1	A
	SCI	C7	29/	0.3	-Jan-88	37.8	A
	MS	NA	31/	8.0	Feb-88	36.5	A
	Dystonia	NA	36/	7.0	-Jan-88	31.8	A
	SCI	C7	25/	2.0	-Apr-88	5.4	D
	Head Inj	NA	42/	3.6	-Apr-88	27.5	A
	MS	NA	45/	6.0	May-88	35.2	A

(a) Primary Diagnosis: MS designates Multiple Sclerosis; SCI designates Spinal Cord Injury

(b) Site of Injury; T designates thoracic; C designates cervical; NA designates not applicable

(c) Date of SynchroMed pump implant

(d) Duration of long-term experience through 4/91 or last follow-up

(e) Patient status as of 4/91. 'A' designates active; 'D' designates dead due to disease; 'Sc' designa

(f) Protocol deviation

(g) Patient died due to progressive disease

ND = No Data

3. PROTOCOL II - MULTICENTER DOUBLE-BLIND, RANDOMIZED STUDY OF INTRATHECAL BACLOFEN VERSUS PLACEBO

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity caused by spinal cord lesions or multiple sclerosis in a multicenter, randomized, double-blind study.

Study Population

Ninety-three patients have been screened, 75 have proceeded to implant. Patient selection was based on the following criteria: males and females between 18 and 65 years of years; patients must have had severe, chronic (>12 months) spasticity as defined by an Ashworth score of three or greater and a spasm frequency score of two or greater; spasticity must have been refractory to oral baclofen or the side effects unacceptable at effective doses; spasticity must have been stable; adequate CSF flow must have been evident; patients must have exhibited a response to a ≤ single bolus 100 µg screening dose before implantation; informed consent must have been given voluntarily.

All patients were screened in a double-blind phase of the study. Those who responded proceeded to pump implantation and the long-term phase of the study. Those who did not respond to screening were not implanted. Table 12 is a summary of patient characteristics. Table 13 lists patient demographic information.

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Table 12. Protocol II - Summary of Patient Characteristics

Factor	
Total Patients	93
Mean Age (years)	40.2
Sex:	
Males	66
Females	27
Duration of Spasticity (years)	7.9 (0.1-34.6)
Diagnosis	
SCI	60
MS	31
Other	2
Follow-up	
Median	14.0
Mean	15.6
Range	4.6-35.3

Study Status

This study was initiated in May 2, 1988. On March 7, 1990 FDA Center for Drug Evaluation and Research authorized Medtronic to proceed with a Treatment Protocol. This has been titled *Protocol IIB-* [redacted] All patients currently enrolled in Protocol II will be "rolled-over" following completion of required follow-up and IRB approval at each institution. Enrollment in Protocol II is complete and this study will be closed when all patients have been "rolled over" to Protocol IIB- [redacted]

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TABLE 13. PROTOCOL II PATIENT DEMOGRAPHICS

Pt. ID	Primary Dx(a)	Site of Injury(b)	Age/Sex	Duration of Spasticity (yrs)	Implant Date(c)	Months Follow-up(d)	Status(e)
	MS	NA	30/	10.0	ay-88	35.3	A
	MS	NA	56/	4.0	un-88	34.2	A
	MS	NA	62/	6.6	A	NA	Sc
	SCI	T4	39/	9.3	an-89	4.6	W
	SCI	C2	38/	8.4	A	NA	Sc
	SCI	T5-8	24/	3.6	pr-89	22.4	A
	SCI	C5	36/	2.7	A	NA	Sc
	SCI	T6-7	36/	15.5	eb-90	12.6	A
	SCI	C6	23/	4.8	pr-89	23.4	A
	SCI	C5	34/	7.8	ay-89	21.2	A
	SCI	C4	30/	5.4	A	NA	Sc
	MS	NA	26/	6.2	A	NA	Sc
	SCI	T6	22/	1.2	ep-89	17.5	A
	SCI	T7	33/	3.3	ec-89	14.4	A
	SCI	T10	25/	1.2	an-90	15.0	A
	SCI	C4	41/	3.7	eb-90	13.8	A
	SCI	C4	39/	2.7	eb-90	12.5	A
	SCI	C4	30/	1.1	pr-90	10.1	A
	SCI	T6	40/	1.0	ug-89	20.7	A
	SCI	C4	32/	4.5	ec-89	13.8	A
	SCI	C6	42/	0.5	ay-90	10.1	A
	NeuroFib	NA	41/	11.0	A	NA	Sc
	SCI	C4-5	29/	9.3	un-90	9.1	a
	MS	NA	37/	17.5	Jul-89	20.4	a
	SCI	C6	25/	3.8	A	NA	Sc
	SCI	T6	57/	2.3	ov-89	10.8	D
	SCI	T9	29/	5.3	ov-88	26.0	A
	MS	NA	42/	10.0	an-89	23.7	A
	SCI	T10	41/	22.9	pr-89	20.5	A
	MS	NA	37/	10.9	pr-89	20.6	A
	SCI	T7-8	31/	12.9	ay-89	22.0	A
	SCI	L3-4	33/	3.9	Jul-89	17.6	A
	MS	NA	44/	19.2	ug-89	16.0	A
	MS	NA	47/	5.7	ar-90	13.4	A
	MS	NA	39/	4.1	ar-90	12.7	A
	MS	NA	49/	11.1	eb-90	13.8	A
	MS	NA	63/	8.0	un-90	9.7	A
	MS	NA	54/	1.8	Jul-90	7.6	A
	MS	NA	33/	9.4	ov-89	17.0	A
	MS	NA	56/	8.1	ov-89	11.2	A
	MS	NA	30/	10.0	an-90	13.0	A
	MS	NA	42/	18.0	eb-90	5.0	A
	MS	NA	46/	25.3	ar-90	8.2	A
	SCI	C7-8	54/	2.4	Oct-88	29.8	A
	SCI	C6	36/	0.1	Jun-89	21.9	A
	SCI	C6-7	34/	2.1	A	NA	Sc
	SCI	C5-6	38/	2.0	A	NA	Sc
	SCI	C4-5	54/	34.0	A	NA	Sc
	SCI	C4-5	25/	2.5	Jan-90	15.2	A

	SCI	C2-7	63/	1.3	NA	NA	Sc
	SCI	T8	38/	9.3	NA	NA	Sc
	SCI	C6	45/	18.5	ɔb-90	14.5	A
	SCI	C4-5	31/	7.2	ar-90	13.1	A
	SCI	C4-5	25/	4.4	ul-90	8.9	A
	SCI	T4	29	7.5	A	NA	Sc
	MS	NA	62	2.7	an-90	14.1	A
	SCI	C6-7	69/	1.1	un-90	10.0	A
	SCI	C6	48	4.9	pr-90	11.6	A
	SCI	C3-4	44/	2.5	lul-90	8.9	A
	SCI	NA	44/	13.5	A	NA	Sc
	SCI	NR	40/	17.9	ov-90	4.7	A
	SCI	C6	27/	5.3	an-89	27.1	A
	Lupus	NA	52/	2.1	lar-89	24.8	A
	MS	NA	44/	15.7	ug-89	19.4	A
	MS	NA	41/	14.3	ep-89	17.7	A
	MS	NA	65/	14.2	lar-09	11.9	A
	MS	NA	37/	6.0	ec-89	15.9	A
	MS	NA	40/	14.4	lov-88	17.5	W
	SCI	L5	50/	5.2	ec-88	26.8	A
	SCI	C4-5	36/	3.8	eb-89	26.2	A
	SCI	C6	43/	0.8	un-89	20.5	A
	SCI	C4-5	28/	13.9	Jul-89	19.2	A
	SCI	T10	30/	4.4	Oct-89	17.9	A
	SCI	T7-10	39/	6.8	Oct-89	15.7	A
	SCI	C5	41/	5.7	Oct-89	16.3	A
	SCI	T6-7	24/	2.3	Apr-90	10.6	A
	SCI	T4-5	26/	1.6	Mar-90	9.2	A
	MS	NA	69	29.5	IA	NA	Sc
	SCI	C5-6	41/	2.3	Apr-90	9.7	A
	MS	NA	53/	14.2	Mar-90	10.6	A
	MS	NA	43	5.2	Mar-90	12.7	A
	MS	NA	62	2.3	Apr-90	10.1	A
	MS	NA	46	20.0	Mar-90	11.2	A
	SCI	T5	52	3.0	Sep-89	17.3	A
	SCI	C4	27	3.1	Sep-89	16.6	A
	SCI	C5	25	1.4	Nov-89	11.7	A
	MS	NA	55	34.6	Mar-90	12.3	A
	SCI	C4	31	1.1	Apr-90	8.1	A
	SCI	C4-5	35	0.5	Jan-90	12.2	A
	SCI	C5	33	2.2	Jun-90	10.5	A
	SCI	C6	19	1.5	NA	NA	NA
	SCI	NA	48	1.6	NA	NA	Sc
	MS	NA	41	9.2	NA	NA	Sc

(a) Primary Diagnosis: MS designates Multiple Sclerosis; SCI designates Spinal Cord Injury

(b) Site of Injury: T designates thoracic; C designates cervical

(c) Date of SynchroMed pump implant

(d) Duration of long-term experience through 4/91 or last follow-up

(e) Patient status as of 4/91, 'A' designates active; 'D' designates dead due to disease; 'Sc' designa screened only, not implanted

(f) Protocol deviation

NA = designates not applicable

4. PROTOCOL IIB - TREATMENT PROTOCOL - MULTICENTER STUDY OF INTRATHECAL BACLOFEN VERSUS PLACEBO (

Objective

The objective of this study is to provide chronic Lioresal® (baclofen, USP) Injection therapy for patients with severe spasticity of spinal cord origin who meet protocol criteria and to obtain additional data on the safety of intrathecally administered Lioresal Injection.

Study Population

Sixty-six patients have been screened, 61 have proceeded to implant. Patient selection was based on the following criteria: patients must have had severe, chronic spasticity as defined by an Ashworth score of three or greater or a spasm frequency score of two or greater; spasticity must have been refractory to oral baclofen or the side effects unacceptable at effective doses; patients must have exhibited a response to a ≤ 100 µg single bolus screening dose before implantation; informed consent must have been given voluntarily. Table 14 summarizes patient characteristics. Table 8 lists patient demographic information.

Table 14. Protocol IIB - Summary of Patient Characteristics

Factor	
Total Patients	66*
Mean Age (years)	39.7 (16-71)
Sex:	
Males	42
Females	23
Duration of Spasticity (years)	9.5 (0.3-62.0)
Diagnosis	
SCI	42
MS	22
Other	1
Follow-up	
Median	4.5
Mean	4.4
Range	0.1-9.9

*Data for patient [redacted] is not available

Study Status

This study was initiated on 7 March 1990 and remains active. Quarterly safety updates are filed with FDA describing results from weekly telephone surveys of newly enrolled patients.

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TABLE 15. PROTOCOL IIB PATIENT DEMOGRAPHICS

Pt. ID	Primary Dx(a)	Site of Injury(b)	Age/Sex	Duration Spasticity	Implant Date(c)	Months Follow-up(d)	Status(e)
	SCI	T11-12	71/	1.9	Jul-90	8.5	A
	MS	NA	27/	NR	Aug-90	7.4	A
	MS	NA	64/	0.7	Sep-90	6.1	A
	MS	NA	23/	8.8	Oct-90	5.1	A
	MS	NA	36/	13.9	Nov-90	4.61	A
	MS	NA	55/	NR	Nov-90	3.98	A
	SCI	T2	52/	33.7	Dec-90	3.42	A
	SCI	C6	51/	4.3	Jan-91	3.45	A
	SCI	T10	43/	1.5	Jan-91	3.29	A
	SCI	NR	21/	5.2	Apr-91	.07	A
	SCI	C5	17/	1.9	Apr-91	.30	A
	SCI	NA	69/	BR	Oct-90	4.5	A
	SCI	NR	55/	1.8	Jan-91	1.64	A
	MS	NA	44/	5.2	May-90	8.2	A
	Familial Spastic Disease	NA	62/	NR	Jun-90	8.9	A
	MS	NA	68/	20.8	Jun-90	7.6	A
	SCI	T8	47/	24.3	Jun-90	9.7	A
	SCI	C3	30/	5.3	May-90	9.9	A
	SCI	C4-5	33/	10.9	Sep-90	4.6	A
	SCI	C4	20/	3.1	Jun-90	8.9	A
	SCI	NR	51/	13.6	Sep-90	6.9	A
	SCI	C1-2	16/	2.4	Sep-90	6.0	A
	SCI	T4	47/	10.02	NA	NA	Sc
	SCI	C5	40/	3.1	Dec-90	3.2	A
	MS	NA	40/	24.9	Dec-90	3.45	A
	SCI	T7-8	63/	1.0	Dec-90	3.68	A
	SCI	C5	27/	3.5	Jan-91	2.01	A
	MS	NA	36/	12.7	NA	NA	Sc
	SCI	T6	25/	1.7	Mar-91	.95	A
	SCI	C5-6	60/	2.6	Aug-90	5.6	A
	SCI	T4	31/	6.3	Aug-90	0.2	A
	SCI	T9	37/	2.9	Mar-90	3.85	A
	SCI	C6	46/	1.8	Dec-90	3.88	A
	MS	NA	48/	24.8	Nov-90	5.0	A
	NA	NA	NA	NA	NA	NA	Sc
	MS	NA	60/	11.6	Aug-90	8.3	A
	MS	NA	29/	4.8	Sep-90	4.8	A
	MS	NA	53/	23.0	Jan-91	1.84	A
	MS	NA	54/	17.0	Feb-91	1.51	A
	MS	NA	53/	5.0	Jan-91	0.10	A
	MS	NA	45/	17.9	Dec-90	4.05	A
	SCI	C5-6	21/	0.3	Aug-90	7.6	A
	SCI	C3-4	26/	0.5	Jun-90	7.6	A

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	SCI	C7	37	2.5		Nov-90	4.6	A
	SCI	T8	24	1.2		Aug-90	7.63	A
	SCI	T4	22	5.6		Dec-90	3.68	A
	SCI	C7	25	5.8		-Jan-90	2.17	A
	SCI	T11-L4	46	9.8		-Apr-90	9.6	A
	MS	NA	24	14.7		-Oct-90	5.0	A
	MS	NA	36	16.6		-Oct-90	5.7	A
	SCI	T5	27	2.1		-Oct-90	5.1	A
	SCI	C1-2	21	5.1		-Oct-90	5.0	A
	SCI	C2-3	29	NR		-Jul-90	8.3	A
	SCI	C3	53	0.9		-Nov-90	5.26	A
	SCI	NR	49	1.8		-Mar-91	.62	A
	SCI	NR	33	3.7		-Mar-91	4.11	A
	SCI	C6	22	1.2		-Dec-91	3.26	A
	SCI	C4-5	24	0.6		-Feb-91	1.74	A
	SCI	C4-5	49	15.2		-Feb-91	.59	A
	SCI	C2	27	0.1		-Oct-90	5.3	A
	MS	NA	32	11.9		-Feb-91	.59	A
	MS	NA	43	10.8		-Dec-90	4.54	A
	SCI	T6	38	2.3		-Mar-91	.66	A
	MS	NA	42	24.0		-Feb-91	.76	A
	MS	NA	50	13.9		NA	NA	Sc
	SCI	C6	34	4.7		NA	NA	Sc

(a) Primary Diagnosis: MS designates Multiple Sclerosis;
SCI designates Spinal Cord Injury
(b) Site of Injury: T designates thoracic; C designates Cervical
(c) Date of SynchroMed pump implant
(d) Duration of experience through last follow-up
(e) Patient status 'A' designates active; 'W' designates withdrawal; 'Sc' designated screened only not implanted
(f) Protocol deviation
(g) Patient [redacted] demographic data missing
NA signifies not applicable

5. PROTOCOL III - DOUBLE-BLIND, RANDOMIZED STUDY OF INTRATHECAL BACLOFEN VERSUS PLACEBO ([redacted]

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity caused by various neurological disorders.

Study Population

This study was conducted by Dr Richard Penn at Rush-Presbyterian-St. Luke's Medical Center under physician sponsored [redacted] Patients enrolled in this study are considered deviations from Protocol II. Entry criteria were identical to those of Protocol II except the "evaluable" patients were given a higher initial screening bolus dose than the protocol stipulates. "Inevaluable" patients included those with spasticity of neurological origins other than spinal cord injury and multiple sclerosis. Table 16 summarizes patient characteristics. Table 17 lists patient demographic information.

Table 16. Protocol III - Summary of Patient Characteristics

Factor	
Total Patients	32
Mean Age (years)	41.0 (12-76)
Sex:	
Males	16
Females	16
Duration of Spasticity (years)	10.6 (0.3-31.1)
Diagnosis	
SCI	11
MS	9
Other	12
Follow-up	
Median	16.2
Mean	15.1
Range	0.1-34.1

Study Status

This study was initiated April 1989. Dr Penn has screened 32 patients and implanted 28. He will continue to enroll patients into this study under his physician sponsored IND.

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TABLE 17. PROTOCOL III INEVALUABLE PATIENT DEMOGRAPHICS

Pt. ID	Primary Dx(a)	Site of Injury(b)	Age/Sex	Duration of Spasticity (yrs)	Implant Date(c)	Months Follow-up(d)	Status(e)
	dystonia	NA	54	16.8	May-88	34.14	A
	SCI	T4-5	57	1.2	Dec-88	21.94	A
	SCI	C5	25	0.5	Nov-88	28.39	A
	cervical myelopathy	C4-6	60	1.4	Nov-88	28.52	A
	neurofibroma	NA	71/	28.3	Apr-89	23.91	A
	MS	NA	46/	21	Apr-89	23.32	A
	arachnoiditis	NA	18/	13.5	-Jul-89	20.79	A
	MS	NA	48/	23	Aug-89	18.91	A
	SCI	C5-6	41/	3	Aug-89	17.76	A
	MS	NA	39/	11.5	Aug-89	19.28	A
	spondylolithesis	NA	40/	2.2	Aug-89	19.64	A
	SCI	C4,T4-5	12/	12.1	Sep-89	.33	W
	MS	NA	44/	13	Sep-89	.03	D
	MS	NA	39/	20	-Oct-89	15.20	A
	SCI	T6-7	50/	1.7	-Oct-89	17.04	A
	MS	NA	56/	19.6	-Oct-89	17.04	A
	traumatic brain injury	NA	18/	0.5	Nov-89	13.39	A
	SCI	T8-12	66/	12.5	Nov-89	16.91	A
	SCI	C5-6	20/	1.7	Dec-89	15.56	A
	MS	NA	41/	15.2	A	NA	Sc
	spasticity unknown origin	NA	76/	7.1	A	NA	Sc
	MS	NA	58/	31.1	-Jan-90	12.96	A
	SCI	T8-9	21/	8.6	-Jan-90	14.21	A
	stiffman syndrome	NA	40/	7.2	-Apr-90	6.02	A
	MS	NA	41/	21.9	-Apr-90	9.93	A
	SCI	C5	35/	13.9	-Apr-90	11.78	A
	dystonia	NA	37/	20.4	A	NA	Sc
	SCI	T4-5	22/	3.1	-Jul-90	8.6	A
	head injury	NA	18/	2.1	-Jul-90	1.68	A
	SCI	C3-4	39/	1.5	-Jun-90	5.1	A
	SCI	C4-7	44/	1.8	-Mar-91	1.1	A
	anoxic	NA	36/	0.3	NA	NA	Sc

(a) Primary Diagnosis: MS designates Multiple Sclerosis; SCI designates Spinal Cord Injury

(b) Site of Injury: T designates throacic; C designates cervical; NA designates not applicable

(c) Date of SynchroMed pump implant

(d) Duration of long-term experience through 3/90 or last follow-up; NA designates not applicable

(e) Patient status as of 3/90. 'A' designates active; 'W' designates withdrawal due to pocket infection; 'Sc' designates screened only, not implanted.

(f) Protocol deviation

NA signifies not applicable

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7. PROTOCOL V - REPORT OF A SINGLE CENTER STUDY OF INTRATHECAL BACLOFEN IN PATIENTS WITH SPINAL CORD INJURY

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity in a single center, randomized, double-blind study.

Study Population

Sixteen patients with severe chronic spasticity due to spinal cord injury were screened and implanted. Oral baclofen was ineffective or caused intolerable side effects. Table 18 summarizes patient characteristics. Table 19 lists patient demographic information.

Table 18. Protocol V - Summary of Patient Characteristics

Factor	
Total Patients	16
Mean Age (years)	35.1 (18-59)
Sex:	
Males	14
Females	2
Duration of Spasticity (years)	5.9 (0.5-18.9)
Diagnosis	
SCI	14
MS	0
Other	1
Follow-up	
Median	13.4
Mean	18.0
Range	1.4-37.0

Study Status

This study was initiated 3 February 1988. Dr Loubser continues to enroll patients at the Institute of Rehabilitation and Research, Houston, Texas under his physician sponsored IND.

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TABLE 19. PROTOCOL V EVALUABLE PATIENT DEMOGRAPHICS							
Pt. ID	Primary Dx(a)	Site of Injury(b)	Age/Sex	Duration of Spasticity (yrs)	Implant Date(c)	Months Follow-up(d)	Status(e)
	SCI	T8	32	8	Feb-88	36.38	A
	SCI	C4	44	0.5	Feb-88	37.01	A
	SCI	C7	59	0.5	Mar-88	34.28	A
	SCI	T8	39	5	Oct-88	29.01	A
	SCI	T7	40	3	Mar-89	24.11	A
	CP	NA	18	18	Aug-89	18.88	A
	SCI	C2	21	4.1	Mar-89	24.80	A
	SCI	T12/L1	53	2.8	Sep-89	16.55	A
	SCI	C4-5	28/	1.3	Jan-90	13.42	A
	SCI	C7	36	7	Jan-90	13.88	A
	SCI	T12	40	6	Aug-90	6.38	A
	SCI	C5	20/	5	Jul-90	8.52	A
	NR	NR	NR	NR	Apr-90	11.12	A
	SCI	C5	21/	4	Aug-90	7.04	A
	SCI	C6	40/	1.5	Jan-91	1.41	A
	SCI	C5-6	36/	.5	Oct-90	5.39	A

(a) Primary Diagnosis: MS designates Multiple Sclerosis; SCI designates Spinal Cord Injury

(b) Site of Injury: T designates thoracic; C designates cervical; L designates lumbar

(c) Date of SynchroMed pump implant

(d) Duration of long term experience through 4/91 or last follow-up

(e) Patient status as of 4/91, 'A' designates active

7. PROTOCOL VIII - DOUBLE-BLIND, RANDOMIZED STUDY OF INTRATHECAL BACLOFEN VERSUS PLACEBO IN THE MANAGEMENT OF SPASTIC CEREBRAL PALSY

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity caused by cerebral palsy in a single center controlled study.

Study Population

This study is being conducted by Dr Richard Penn at Rush-Presbyterian-St. Luke's Medical Center under physician sponsored Pediatric patients with cerebral palsy are candidates for enrollment. Table 20 summarizes patient characteristics. Table 21 lists patient demographic information.

Table 20. Protocol VIII - Summary of Patient Characteristics

Factor	
Total Patients	3
Mean Age (years)	11.7 (11-13)
Sex:	
Males	2
Females	1
Duration of Spasticity (years)	11.9 (11.1-13.1)
Diagnosis	
SCI	0
MS	0
CP	3
Follow-up	
Median	9.6
Mean	9.6
Range	8.8-10.3

Study Status

This study was initiated April 1989. Dr Penn has enrolled three patients thus far. He will continue to enroll patients into this study under his physician sponsored IND.

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TABLE 21. PROTOCOL VIII PATIENT CHARACTERISTICS							
Pt. ID	Primary Diagnosis(a)	Site of Injury	Age/Sex	Duration of Spasticity	Implant Date(b)	Months Follow-up(c)	Status(d)
[redacted]	CP	NA	11/[redacted]	11.1	[redacted]Apr-90	10.33	A
	CP	NA	11/	11.4	Jul-90	8.82	A
	CP	NA	13	13.07	NA	NA	Sc

(a) Primary Diagnosis: CP designates cerebral palsy

(b) Date of SynchroMed pump implant

(c) Duration of experience through last follow-up

(d) Patient statu 'A' designates active; 'Sc' designates screened only, not implanted

NA signifies not applicable

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8. PROTOCOL VI - DOUBLE-BLIND, RANDOMIZED CROSS-OVER TRIAL OF INTRATHECAL BACLOFEN VERSUS PLACEBO IN THE MANAGEMENT OF SPASTIC CEREBRAL PALSY

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity caused by cerebral palsy in a single center controlled study.

Study Population

This study is being conducted by Dr. Leland Albright at Children's Hospital, Pittsburgh, PA. Thirty-six patients have been screened, 18 have been implanted. Table 22 summarizes patient characteristics. Table 23 lists patient demographic information.

Table 22. Protocol VI - Summary of Patient Characteristics

Factor	
Total Patients	36
Mean Age (years)	13.4 (5 - 31)
Sex:	
Males	24
Females	12
Duration of Spasticity (years)	11.1 (0.5 - 26)
Diagnosis	
CP	32
HI	4
Follow-up	
Median	11
Mean	11.1
Range	0.5 - 27

Study Status

This study was initiated February 1989. Dr Albright has enrolled 18 patients thus far. He will continue to enroll patients into this study under his physician sponsored IND.

TABLE 23. PROTOCOL VI PATIENT DEMOGRAPHICS						
ID ##	Dx(a)	AGE/SEX	YEARS SINCE Dx	IMPLANT DATE(d)	MONTHS FOLLOW-UP(e)	STATUS(f)
	CP	26/	25	Feb-89	27	A
	CP	18/	16	Jun-89	23	A
	CP	18/	17	Oct-89	19	A
	CP	8/	7	Nov-89	14	T
	HI	26/	3	Nov-89	14	T
	CP	9/	8	Jul-89	19	T
	HI	20/	2	Feb-89	27	A
	CP	14/	13	Aug-89	21	A
	CP	8/	7	NA	NA	Sc ONLY
	CP	11/	10	Jun-90	11	A
	CP	11/	10	Jun-90	11	A
	CP	15/	13	NA	NA	Sc ONLY
	CP	5/	5	May-89	3	T
	CP	14/	13	NA	NA	Sc ONLY
	CP	7/	6	NA	NA	Sc ONLY
	CP	12/	12	NA	NA	Sc ONLY
	CP	5/	5	NA	NA	Sc ONLY
	CP	9/	9	Aug-90	0.5	T
	CP	15	15	Feb-91	3	A
	CP	13/	13	Jan-91	4	A
	CP	19/	19	Mar-91	2	A
	CP	10	10	NA	NA	Sc ONLY
	CP	12/	11	NA	NA	Sc ONLY
	CP	18/	18	NA	NA	Sc ONLY
	CP	5.5	5.5	NA	NA	Sc ONLY
	CP	31	26	NA	NA	Sc ONLY
	CP	9/	9	NA	NA	Sc ONLY
	CP	7/	7	NA	NA	Sc ONLY
	CP	15/	15	NA	NA	Sc ONLY
	CP	9/	9	Sep-90	8	A
	HI	10	1	Dec-90	5	A
	CP	17/	17	NA	NA	Sc ONLY
	CP	6/	5	Mar-91	2	A
	HI	16.5	.5	NA	NA	Sc ONLY
	CP	12	11	na	NA	Sc ONLY
	CP	23	23	NA	NA	Sc ONLY

(a) Diagnosis: CP designates Cerebral Palsy, HI designates post traumatic head injury; CSA designates congenital skull agenesis

(b) Therapy given prior to study entry to affect functional status.

(c) Oral anti-spasticity medication administered to patients prior to entry.

(d) Date of SynchroMed pump implant.

(e) Duration of long-term experience through 4/91 or last follow-up

(f) Patient status as of 4/91, 'A' designates active, 'Sc' designates screened only, not implanted, 'T' designates patient terminated study

NA = Not Applicable

NR = Not Recorded

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European Studies

1. PROTOCOL IV - REPORT OF AN OPEN-LABEL, LONG-TERM SAFETY AND EFFICACY TRIAL OF INTRATHECAL BACLOFEN CONDUCTED IN EUROPE

Objective

To evaluate the safety and efficacy of intrathecal baclofen in the treatment of severe spasticity in a multicenter, open-label trial conducted in Europe.

Study Population

Twenty-eight patients with severe chronic spasticity due to spinal cord injury or multiple sclerosis were enrolled. Oral baclofen was ineffective or caused intolerable side effects. Table 24 summarizes patient characteristics. Table 25 lists patient demographic information.

Table 24. Protocol IV - Summary of Patient Characteristics

Factor	
Total Patients	28
Mean Age (years)	46.4 (20-64)
Sex:	
Males	16
Females	12
Duration of Spasticity (years)	NA
Diagnosis	
SCI	18
MS	10
CP	0
Follow-up	
Median	42.0
Mean	42.5
Range	7-60

Study Status

This study was initiated 1 December 1986 and completed 30 September 1988. Patients are currently being followed in a European market surveillance program.

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TABLE 25. PROTOCOL IV PATIENT DEMOGRAPHICS					
Pt. ID	Center	Diagnosis(a)	Age/Sex	Implant Date	Follow-up (mos)
	2	MS	37/	Dec-86	50
	2	SCI	64/	Sep-86	53
	1	MS	61/	Nov-86	48
	1	MS	46/	Apr-86	58
	1	MS	26/	Jul-86	56
	1	MS	59/	Feb-86	60
	1	SCI	33/	Dec-86	50
	1	SCI	43/	Apr-87	46
	1	MS	50/	Apr-87	46
	2	SCI	27/	May-87	46
	3	SCI	52/	Apr-87	46
	4	SCI	39/	Jul-87	43
	4	SCI	62/	Jul-87	43
	3	SCI	40/	Aug-87	42
	1	MS	56/	May-87	45
	2	MS	46/	Sep-87	41
	1	MS	56/	Sep-87	41
	1	MS	60/	Aug-87	42
	2	SCI	63/	Jan-88	7
	3	SCI	50/	Jan-88	37
	3	SCI	47/	Dec-87	39
	1	SCI	57/	Dec-87	38
	1	SCI	47/	Dec-87	38
	3	SCI	36/	Mar-88	35
	1	SCI	20/	Feb-88	25
	4	SCI	49/	Jan-88	37
	4	SCI	48/	Feb-88	36
	4	SCI	24/	Nov-87	41

(a) MS = Multiple sclerosis; SCI = spinal cord injury

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2. PROTOCOL VII - REPORT OF A EUROPEAN MARKET SURVEILLANCE

Objective

To monitor the safety of intrathecal baclofen in the treatment of spasticity in actual clinical practice in Europe.

Study Population

This patient population is derived from several investigators in Europe where baclofen is supplied by several manufacturers though none are conducting clinical trials. In addition, the Medtronic SynchroMed Infusion is commercially available in Europe and may be purchased for intraspinal infusion of medications. Physicians administering baclofen therapy in this setting did not adhere to a consistent prospective protocol. Table 26 summarizes patient characteristics. Table 27 lists patient demographic information.

Table 26. Protocol VII - Summary of Patient Characteristics

Factor	
Total Patients	165
Mean Age (years)	40.5* (12-72)
Sex:	
Males	96
Females	69
Duration of Spasticity (years)	NA
Diagnosis	
SCI	49
MS	66
other	45
unknown	5
Follow-up	
Median	23.5
Mean	22.1
Range	1-59

*Age missing for patients CH3'1 and CH3'2

Study Status

This study was initiated June 1987. A total of 166 patients have been screened and 164 have been implanted. Medtronic continues to monitor activity in Europe.

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TABLE 27. PROTOCOL VII PATIENT DEMOGRAPHICS				
Pt. ID	Age/Sex	Primary Diagnosis(a)	Implant Date (d/m/y)(b)	Duration of Follow-up (months)(c)
	15/	NA	ul-89	17
	49	Encephalitis	an-90	12
	25	Brain trauma	an-90	13
	20/	Cerebral trauma	ay-90	9
	12	Cerebral trauma	ay-90	9
	27	Spinal hemiangioma	un-88	32
	24	SCI	un-88	32
	33	Hydromyely	ay-89	21
	49	MS	ec-89	14
	44/	MS	eb-90	12
	45/	MS	(d)	NA
	49/	MS	ug-90	6
	34/	Cerebral trauma	un-88	32
	20/	Iatrogenic	un-88	32
	20/	SCI	32489	26
	23/	Strumpell Lorrain	ec-88	26
	45	MS	Oct-89	16
	56/	Cerebral trauma	eb-90	11
	61	MS	ug-90	6
	62	MS	ep-90	4
	39	Strumpell Lorrain	lay-88	33
	38	MS	un-88	32
	43/	SCI	un-88	32
	62/	SCI	eb-89	24
	24/	SCI	eb-89	24
	12/	SCI	Mar-89	23
	57/	Cerebral trauma	Apr-89	22
	41/	MS	Jun-89	20
	31/	SCI	Oct-89	15
	40/	MS	Jan-90	13
	52	Cerebral hemiplegia	eb-90	12
	72/	Hemiplegia post Vase-accident	Mar-90	11
	38/	Cerebral trauma	Mar-90	11
	61/	SCI	Apr-90	10
	68/	Vascular hemiplegia	Apr-90	10
	48/	SCI	Sep-88	17
	28/	SCI	Jun-88	32
	19/	SCI	Jan-89	25
	40	MS	Nov-87	39
	53/	SCI	Nov-87	39
	35	MS	Feb-89	38
	63/	Strumpell Lorrain	Jun-88	35
	40	MS	Nov-88	27

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	34	MS	Nov-88	27
	35	MS	Feb-89	24
	21	Strumpell Lorrain	Jun-88	32
	29	SCI	NA	51
	27	Cerebral palsy	NA	21
	56	MS	NA	26
	26	SCI	Feb-86	59
	37	MS	Jun-87	45
	51	MS	NA	37
	43	Ischemia	Jan-88	37
	30	SCI	NA	36
	43	MS	NA	34
	14	Myelitis	NA	32
	40	MS	NA	26
	51	MS	May-88	33
	20	SCI	Jul-88	31
	35	SCI	Oct-88	25
	34	SCI	Sep-88	29
	25	SCI	Nov-88	27
	49	MS	Nov-88	27
	38	Friedreich's Disease	Apr-89	23
	48	MS	Jan-89	25
	23	SCI	May-89	21
	26	SCI	Apr-89	10
	60	SCI	Feb-90	7
	38	MS	Feb-88	36
	38	MS	Mar-88	35
	33	SCI	Dec-88	26
	25	SCI	Jun-88	32
	34	SCI	Sep-88	29
	34	SCI	Mar-89	26
	41	Tumor	Apr-89	22
	23	SCI	Sep-89	17
	48	MS	Jan-89	20
	61	MS	Apr-88	34
	50	MS	May-88	33
	46	Cerebral trauma/MS	Jun-88	32
	48	MS	Jul-88	31
	53	MS	Aug-88	30
	48	MS	Sep-88	29
	49	MS	Oct-88	28
	45	MS	Nov-88	27
	45	MS	Jan-89	25
	48	MS	Jan-89	11.5
	52	MS	Mar-89	23
	19	Cerebral trauma	Apr-89	22
	33	MS	Apr-89	22
	47	MS	Jun-89	20

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	41/	MS	-Jul-89	19
	44/	MS	-Jul-89	19
	33/I	Vasc. Myelopathy	-Jul-89	19
	70/	SCI	-Jul-89	19
	31/I	SCI	Aug-89	18
	47/I	MS	Oct-89	17
	49/	MS	Oct-89	17
	59/	Spinal meningeoma	Nov-89	16
	34/	MS	Nov-89	16
	47/	MS	Dec-89	15
	52/I	MS	Jan-90	13
	49/	MS	Feb-90	12
	53/	MS	Mar-90	11
	47/	MS	Apr-90	10
	50/	MS	May-90	9
	46/	MS	-Jul-90	8
	68/	MS	-Jul-90	8
	52/	MS	Jan-90	13
	58/	AV-angioma	Oct-90	14
	57/	Stiff man Syndrome	Dec-89	15
	67/	Brain infarctus	Jan-89	25
	15/	Cerebral diplegia	Jan-89	25
	62/	SCI	Mar-88	35
	65/	MS	Mar-88	35
	27/	SCI	Jun-87	44
	44/	Spastic paraplegia	Nov-90	3
	33/	SCI	-Jul-90	8
	27/	SCI	Nov-87	39
	53/	MS	Dec-87	38
	50/	SCI	Jan-88	37
	52/	MS	May-88	43
	32/	SCI	NA	NA
	32/	Cerebral trauma	Aug-88	30
	62/	MS	Aug-88	30
	15/	Cerebral trauma	Nov-88	27
	58/	SCI	Dec-88	26
	32/	Cerebral trauma	Dec-88	26
	38/	Cerebral trauma	Apr-89	22
	29/	Cerebral Paralysis	May-89	21
	28/	MS	Jun-89	20
	27/	SCI	NA	NC
	60/	SCI	NA	NC
	42/	SCI	NA	NC
	33/	SCI	NA	NC
	56/	Encephaloneuritis	Oct-87	40
	59/	MS	Dec-87	38
	53/	MS	Jun-88	32
	53/	MS	Jan-89	25

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	53/	MS		Apr-89	21
	25/	Idiopathic spastic paraparesia		ug-89	18
	24/	Strumpell Lorrain		lov-89	16
	45/	Cervical myelopathy		Mar-90	11
	58/	SCI		Mar-88	35
	53/	MS		lov-87	39
	31/	SCI		May-88	33
	34/	NA		IA	NA
	42/	NA		IA	NA
	44/	SCI		May-88	33
	43/	MS		May-88	33
	41/	Brain infarctus		Jan-89	25
	29/	SCI		Jan-89	25
	50/	SCI		May-89	21
	19/	SCI		lov-89	15
	37/	Cerebral trauma		May-90	9
	48/	Myelopathy		May-88	33
	43/	NA		Jun-90	9
	53/	MS		May-89	21
	42/	MS		lov-89	16
	44/	NA		May-90	9
		SCI		Feb-90	12
		SCI		)ec-89	14
	47	Cerebral vascular infarctus		Jun-90	8
	52	SCI		Jan-91	1
	26	MS		)ec-90	3

(a) SCI= Spinal cord injury; MS = Multiple sclerosis
(b) Date of SynchroMed pump implant
(c) Duration of long term experience through 8/90 or last follow-up
NA = Not Available

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B. Comprehensive Summary of System Complications

Performance of the SynchroMed Infusion System through 1 April 1991 is reported for studies conducted in the U.S. and in Europe. The data has been summarized for 1) U.S. monitored studies only and 2) European studies U.S. studies have been collapsed and reported separately because they have been carefully monitored by Medtronic. The SynchroMed is commercially available in Europe and may be purchased by physicians for spinal applications. Rigorous methods of data collection was not possible in all cases. Performance within each individual study is also presented.

In October 1985, a device design modification was made to correct a passive leak from the pump. Also, initial implants used an earlier catheter version which was subsequently replaced by the Model 8703. System complications occurring in the earlier pump design or catheter have been noted in the tables of complications.

1. U.S. Monitored Studies

a. Comprehensive Summary

U.S. monitored studies are all baclofen studies conducted in the U.S. with the exception of Protocol VI. Though Protocol VI (A Single Center Study of Intrathecal Baclofen Versus Placebo in the Management of Spastic Cerebral Palsy, Dr Albright) was conducted in the U.S. and monitored by Medtronic, it is from the comprehensive summary table of device complications (Table 30) to maintain consistency with the reporting format of Medtronic's pending NDA application [redacted] Clinical Data Amendment, 6 May 1991). Data from this study is reported in Table 35.

Table 28 summarizes the distribution of system complications observed in U.S. Monitored Studies. These are stratified by SynchroMed System component; pump, catheter, access port, and programmer. Pump pocket complications are also included.

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Of 214 patients implanted, 205 are evaluable for system performance because they were implanted with the current system configuration. Nine patients were implanted prior to October 1985 with prototype devices. A total of 14.6% have reported at least one complication related to the system.

Table 29 further stratifies complications within each system component according to description of the complication.

Table 30 is a comprehensive summary of all device complications observed in U.S. monitored studies.

Table 28. Distribution of System Complications - U.S. Monitored Studies

	N	%
Patients Implanted	214	NA
Patients Implanted With Pump/Catheter Prototype	9	NA
Patients Evaluated	205	100
Patients Reporting System Complications	30	14.6
Total System Complications	33	16.1
System Component		
Pump	4	1.9
Catheter	27	13.2
Access Port	1	0.5
Programmer	0	0
Pocket	1	0.5
Total	33	16.1

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Table 29. Summary of System Complications - U.S. Monitored Studies

	N	%
Number of Patients Implanted	214	NA
Number Implanted With Pump/Catheter Prototype	9	NA
Number of Patients Evaluated	205	16.1
Complication Description		
Catheter Angulation	10	4.9
Catheter Occlusion	6	2.9
Catheter Break	5	2.4
Catheter Dislodgement	4	2.0
Pump Stall	2	1.0
Pump Catheter Port Occluded	1	0.5
Pump Underinfusion	1	0.5
Port Connector Kink	1	0.5
Catheter Disconnect	1	0.5
Pocket Infection	1	0.5
Hygroma	1	0.5
Total	33	16.1

The most common system complications observed have been those related to catheter performance. A retrospective comparison was made of Medtronic Model 8703 Spinal Catheter to other commercially available spinal catheters. Information for commercially available catheters was obtained from the scientific literature. A complete reference listing is provided in Appendix I.

The results of this comparision are summarized in Table 30 on the following page.

Table 30. Comparision of Spinal Catheter Performance

	Model 8703	Commercial[a]	
Total Catheters Evaluated	205	383	
Total Months Experience	3711	1379	
Complication Type			
Catheter Kink	10	17	
Catheter Occlusion	6	17	
Catheter Break/Leak	5	5	
Catheter Dislodgement	4	0	
Catheter Disconnect	1	0	
Hygroma	1	8	
Total	27	47	
Complications per Catheter	13.2%	12.3%	p = 0.75
Complications per Month	0.6%	3.4%	p < 0.001

[a] Literature References

Auld AW; Spine, 1985
Plummer JL; Pain, 1991
Shetter AG; J Neurosurg, 1982
Onofrio BM; Mayo Clin Proc, 1981
Krames ES; Cancer, 1985
Greenberg HS; J Neurosurg, 1982
Coombs DW; Can Anesth Soc, 1983
Woods WA; Anesth, 1982
Penn RD; J Neurosurg, 1987
Leavens ME; J Neurosurg, 1982
Harbaugh RE; J Neurosurg, 1982
Delhaas EM; Lancet, 1984
Cobb CA; Surg Neurol, 1984

Table 31. Device Related Complications - U.S. Monitored Studies

	Pre 10/85		Post 10/85		Total	
	N	%	N	%	N	%
Number of patients evaluated*	9	NA	205	NA	214	NA
PROCEDURAL COMPLICATIONS						
Reservoir contamination	0	0.0	23	11.2	23	10.8
Catheter dislodgement	1	22.2	8	3.9	9	4.2
CSF leak/headache	0	0.0	2	1.0	2	0.9
Catheter disconnection	2	22.2	2	1.0	4	1.9
Catheter lacerated	1	11.1	4	2.0	5	2.3
Pocket infection/erosion/revision	1	11.1	6	2.9	7	3.3
Programming error	0	0.0	2	1.0	2	1.0
Meningitis	0	0.0	3	1.5	3	1.4
Catheter reposition	0	0.0	3	1.5	3	1.4
Refill error	0	0.0	3	1.5	3	1.4
Seroma/hematoma	0	0.0	4	2.0	4	1.9
Catheter angulation	0	0.0	6	2.9	6	2.8
Catheter puncture	0	0.0	2	1.0	2	1.0
Catheter break (prior to implant)	0	0.0	1	0.5	1	0.5
Subcutaneous catheter fragment	0	0.0	1	0.5	1	0.5
Wound dehiscence	1	11.1	0	0.0	1	0.5
Pump site discomfort	0	0.0	1	0.5	1	0.5
Pump inverted at implant	0	0.0	1	0.5	1	0.5
Subtotal	6	66.7	72	35.1	78	36.4
SYSTEM COMPLICATIONS						
Catheter angulation	8	88.9	10	4.9	18	8.4
Pump stall	1	11.1	2	1.0	3	1.4
Catheter break	0	0.0	5	2.4	5	2.3
Pocket infection/erosion	0	0.0	1	0.5	1	0.5
Catheter occlusion	0	0.0	6	2.9	6	2.8
Pump underinfusion	0	0.0	1	0.5	1	0.5
Pump overinfusion	2	22.2	0	0.0	2	0.9
Catheter disconnect	0	0.0	1	0.0	1	0.5
Catheter dislodgement	0	0.0	4	2.0	4	1.9
Pump intermittent alarm	1	11.1	0	0.0	1	0.5
Port connector kink	0	0.0	1	0.5	1	0.5
Occluded catheter port	0	0.0	1	0.0	1	0.5
Hygroma	0	0.0	1	0.5	1	0.5
Subtotal	12	133	33	20.0	45	21.0

*To maintain consistency with the reporting format in Medtronic's pending NDA application, information for Protocol VI is provided separately in Table 38

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b. Individual Study Summaries

Each U.S. monitored study is presented individually in Tables 32-38.

TABLE 32. PROTOCOL IB - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	12	
Catheter Break	1	
Catheter Occlusion	2	
Overinfusion	2	
Pump Stall	2	
Intermittent Alarm	1	
Total	20	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Reservoir Contamination	20	
Catheter Disconnection	4	
Catheter Dislodgement	2	
Catheter Lacerated	1	
Catheter Break at implant	1	
Removal of Subcut. Cath. Fragement	1	
Catheter Repositioned	1	
Pocket Infection/Erosion/ Revision	2	
Seroma Hematoma	1	
Wound Dehiscence	1	
Programming Error	1	
Total	35	
Grand Total	55	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.
[c] Prototype design manufactured prior to October, 1985.
[d] Reservoirs treated with gentamicin, pumps not replaced

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TABLE 33. PROTOCOL II - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	4	
Catheter Break	3	
Catheter Dislodged	2	
Catheter Occlusion	2	
Catheter Disconnect	1	
Port Connector Kink	1	
Pocket Infection	1	
Pump Stall	1	
Pump Underinfusion	1	
Total	16	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Catheter Dislodgement	6	
Catheter Angulation	3	
Catheter Lacerated	2	
Pocket Infection/Erosion	3	
Pocket Seroma	1	
Pump Site Discomfort	1	
CSF Leak	1	
Refill Error	1	
Total	18	
Grand Total	34	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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TABLE 34. PROTOCOL IIB - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	1	
Occluded Catheter Port	1	
Hygroma	1	
Total	3	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Catheter Angulation	1	
Catheter Repositioned	1	
Pocket Infection/Erosion	1	
Pocket Seroma	2	
Pump Placed Inverted At Implant	1	
Refill Error	1	
Programming Error	1	
Total	8	
Grand Total	11	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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TABLE 35. PROTOCOL III - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	1	
Catheter Occlusion	1	
Catheter Dislodgement	1	
Total	3	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Meningitis	3	
Reservoir Contamination	3	
Catheter Puncture	2	
Catheter Lacerated	2	
Catheter Dislodgement	1	
Catheter Reposition	1	
Pocket Infection	1	
Total	13	
Grand Total	16	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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TABLE 36. PROTOCOL V - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Break	1	
Catheter Dislodgement	1	
Total	2	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Catheter Angulation	2	
CSF Leak/Headache	1	
Refill Error[c]	1	
Total	4	
Grand Total	6	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.
[c] Pump reservoir not accessed, patient lost effect until reservoir refilled.

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TABLE 37. PROTOCOL VIII - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Occlusion	1	
Total	1	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
None	NA	NA

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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TABLE 38. PROTOCOL VI - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Dislodgement	1	
Total	1	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
CSF Leak	3	
Catheter Dislodgement	1	
Catheter Punture	1	
Wound Dehiscence	1	
Pocket Seroma	1	
Meningitis	1	
Pump Implanted Inverted	1	
Infection, back incision	1	
Total	11	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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2. European Studies

The SynchroMed Infusion System is commercially available in Europe. Medtronic is conducting market surveillance activities to collect information on system performance. Tables 39 and 40 summarize complications from Protocols IV and VII which were conducted in Europe.

TABLE 39. PROTOCOL IV - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	2	
Pump Stall[c]	2	
Total	4	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Catheter Disconnection	1	
Catheter Dislodgement	1	
CSF Leak	1	
Pocket Erosion	1	
Total	4	
Grand Total	8	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.
[c] Prototype design manufactured prior to October, 1985

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TABLE 40. PROTOCOL VII - SUMMARY OF DEVICE RELATED COMPLICATIONS

System Complications[a]

Type of Complication	Number	Patient Identification
Catheter Angulation	2	
Catheter Break	2	
Catheter Occlusion	2	
Pocket Erosion	2	
Pocket Infection	2	
Catheter Dislodgement	1	
Serom/Hematoma	1	
Total	12	

Procedural Complications[b]

Type of Complication	Number	Patient Identification
Catheter Dislodgement	5	
CSF Leak	5	
Programming Error	2	
Catheter Angulation	1	
Pocket Infection	1	
Total	14	
Grand Total	26	

[a] Directly attributable to device design or manufacture.
[b] Directly attributable to surgical procedure error.

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3. Comprehensive Summary of U.S. and European Studies

Experience from U.S. monitored studies and from European studies have been merged into a comprehensive summary table. Table 41 describes world-wide experience from a total of 406 patients implanted. Table 41 does not include Protocol VI.

Table 41. DEVICE RELATED COMPLICATIONS U.S. AND EUROPEAN STUDIES

	PRE 10/85		POST 10/85		TOTAL	
	N	%	N	%	N	%
Number of patients evaluated	24	NA	382	NA	406	NA
PROCEDURAL COMPLICATIONS						
Reservoir contamination	0	0.0	23	6.0	23	5.7
Catheter dislodgement	3	12.5	15	3.9	18	4.4
CSF leak/headache	0	0.0	8	2.1	8	2.0
Catheter disconnection	3	12.5	3	0.8	6	1.5
Catheter lacerated	1	4.2	5	1.3	6	1.5
Pocket infection/erosion/revision	2	8.3	4	1.0	6	1.5
Programming error	0	0.0	4	1.0	4	1.0
Meningitis	0	0.0	3	0.8	3	0.7
Catheter reposition	0	0.0	3	0.8	3	0.7
Refill error	0	0.0	3	0.8	3	0.7
Seroma/hematoma	0	0.0	2	0.5	2	0.5
Catheter kink	0	0.0	2	0.5	2	0.5
Catheter break (implant)	0	0.0	1	0.3	1	0.2
Subcutaneous catheter fragment	0	0.0	1	0.3	1	0.2
Pump site discomfort	0	0.0	1	0.3	1	0.2
Pump inverted at implant	0	0.0	1	0.3	1	0.2
Subtotal	9	37.5	79	20.7	88	21.7
SYSTEM COMPLICATIONS						
Catheter angulation	9	37.5	17	4.4	26	6.4
Pump stall	4	16.7	5	1.3	9	2.2
Catheter break	0	0.0	7	1.8	7	1.7
Pocket infection/erosion	0	0.0	8	2.1	8	2.0
Catheter occlusion	0	0.0	7	1.8	7	1.7
Seroma/hematoma	0	0.0	3	0.8	3	0.7
Pump underinfusion	0	0.0	2	0.5	2	0.5
Pump overinfusion	2	8.3	0	0.0	2	0.5
Catheter puncture	0	0.0	2	0.5	2	0.5
Catheter dislodgement	0	0.0	2	0.5	2	0.5
Pump intermittent alarm	1	4.2	0	0.0	1	0.2
Wound dehiscence	1	4.2	0	0.0	1	0.2
Hygroma	0	0.0	1	0.3	1	0.2
Subtotal	17	70.8	54	14.1	71	17.5
Grandtotal	26	70.8	133	34.8	159	39.2

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APPENDIX 1

Appendix 1

J-1131a

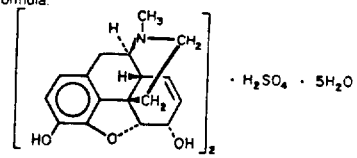
ELKINS-SINN, INC.

INFUMORPH™ 200
INFUMORPH™ 500 CII

(Preservative-free Morphine Sulfate Sterile Solution) For Use in Continuous Microinfusion Devices

DESCRIPTION

Morphine is the most important alkaloid of opium and is a phenanthrene derivative. It is available as the sulfate salt having the following structural formula:



7,8-Didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3,6-diol sulfate (2:1) (salt), pentahydrate

$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ Molecular Weight is 758.83

INFUMORPH™ is a sterile, nonpyrogenic, isobaric, **high potency solution of morphine sulfate**, free of antioxidants, preservatives or other potentially neurotoxic additives. **INFUMORPH™ is intended for use in continuous microinfusion devices for intraspinal administration in the management of pain.**

Each 20 mL ampul of **INFUMORPH™ 200** contains morphine sulfate, USP 200 mg or 10 mg/mL (Warning: May be habit forming) and sodium chloride 8 mg/mL in Water for Injection, USP. Each 20 mL ampul of **INFUMORPH™ 500** contains morphine sulfate, USP 500 mg or 25 mg/mL (Warning: May be habit forming) and sodium chloride 6.25 mg/mL in Water for Injection, USP. If needed, sodium hydroxide and/or sulfuric acid are added for pH adjustment to 4.5. Ampuls are sealed under nitrogen. Each 20 mL DOSETTE® ampul of **INFUMORPH™** is intended for **single use only**. *Discard any unused portion.* DO NOT HEAT-STERILIZE.

CLINICAL PHARMACOLOGY

Morphine produces a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility and physical dependence. Opiate analgesia involves at least three anatomical areas of the central nervous system: the periaqueductal-periventricular gray matter, the ventromedial medulla and the spinal cord. A systemically administered opiate may produce analgesia by acting at any, all or some combination of these distinct regions. Morphine interacts predominantly with the μ-receptor. The μ-binding sites of opioids are very discretely distributed in the human brain, with high densities of sites found in the posterior amygdala, hypothalamus, thalamus, nucleus caudatus, putamen and certain cortical areas. They are also found on the terminal axons of primary afferents within laminae I and II (substantia gelatinosa) of the spinal cord and in the spinal nucleus of the trigeminal nerve.

Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after *intravenous* dosage. Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. A blood-brain barrier exists, and when morphine is introduced outside of the CNS (e.g., *intravenously*), plasma concentrations of morphine remain higher than the corresponding CSF morphine levels. Conversely, when morphine is injected into the *intrathecal space*, it diffuses out into the systemic circulation slowly, accounting for the long duration of action of morphine administered by this route.

Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h (liters/kilogram/hour) in postoperative patients, but shows considerable interindividual variation. The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10% in the feces. Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours, although the longer half-lives were obtained when morphine levels were monitored over protracted periods with very sensitive radioimmunoassay methods. The accepted elimination half-life in normal subjects is 1.5 to 2 hours.

"Selective" blockade of pain sensation is possible by neuraxial application of morphine. In addition, duration of analgesia may be much longer by this route compared to systemic administration. However, CNS effects, associated with systemic administration, are still seen. These include respiratory depression, sedation, nausea and vomiting, pruritus and urinary retention. In particular, both early and late respiratory depression (up to 24 hours post dosing) have been reported following neuraxial administration. Circulation of the spinal fluid may also result in high concentrations of morphine reaching the brain stem directly.

The incidence of unwanted CNS effects, including delayed respiratory depression, associated with neuraxial application of morphine, is related to the circulatory dynamics of the epidural venous plexus and the spinal fluid. The lipid solubility and degree of ionization of morphine plays an important part in both the onset and duration of analgesia and the CNS effects. Morphine has a pK_a 7.9, with an octanol/water partition coefficient of 1.42 at pH 7.4. At this pH, the tertiary amino group in each of the opioids is mostly ionized, making the molecule water soluble. Morphine, with additional hydroxyl groups on the molecule, is significantly more water soluble than any other opioid in clinical use.

Morphine, injected into the *epidural space*, is rapidly absorbed into the general circulation. Absorption is so rapid that the plasma concentration-time profiles closely resemble those obtained after intravenous or intramuscular administration. Peak plasma concentrations averaging 33-40 ng/mL (range 5-62 ng/mL) are achieved within 10 to 15 minutes after administration of 3 mg of morphine. Plasma concentrations decline in a multiexponential fashion. The terminal half-life is reported to range from 39 to 249 minutes (mean of 90 ± 34.3 min) and, though somewhat shorter, is similar in magnitude as values reported after intravenous and intramuscular administration (1.5-4.5 h). CSF concentrations of morphine, after epidural doses of 2 to 6 mg in postoperative patients, have been reported to be 50 to 250 times higher than corresponding plasma concentrations. The CSF levels of morphine exceed those in plasma after only 15 minutes and are detectable for as long as 20 hours after the injection of 2 mg of epidural morphine. Approximately 4% of the dose injected epidurally reaches the CSF. This corresponds to the relative minimum effective epidural and intrathecal doses of 5 mg and 0.25 mg, respectively. The disposition of morphine in the CSF follows a biphasic pattern, with an early half-life of 1.5 h and a late phase half-life of about 6 h. Morphine crosses the dura slowly, with an absorption half-life across the dura averaging 22 minutes. Maximum CSF concentrations are seen 60-90 minutes after injection. Minimum effective CSF concentrations for postoperative analgesia average 150 ng/mL (range <1-380 ng/mL).

The *intrathecal route* of administration circumvents meningeal diffusion barriers and, therefore, lower doses of morphine produce comparable analgesia to that induced by the epidural route. After intrathecal bolus injection of morphine, there is a rapid initial distribution phase lasting 15-30 minutes and a half-life in the CSF of 42-136 min (mean 90 ± 16 min). Derived from limited data, it appears that the disposition of morphine in the CSF, from 15 minutes postintrathecal administration to the end of a six-hour observation period, represents a combination of the distribution and elimination phases. Morphine concentrations in the CSF averaged 332 ± 137 ng/mL at 6 hours, following a bolus dose of 0.3 mg of morphine. The apparent volume of distribution of morphine in the intrathecal space is about 22 ± 8 mL.

Time-to-peak plasma concentrations, however, is similar (5-10 min) after either epidural or intrathecal bolus administration of morphine. Maximum plasma morphine concentrations after 0.3 mg intrathecal morphine have been

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reported from <1 to 7.8 ng/mL. The minimum analgesic morphine plasma concentration during Patient-Controlled Analgesia (PCA) has been reported as 20-40 ng/mL, suggesting that any analgesic contribution from systemic redistribution would be minimal after the first 30-60 minutes with epidural administration and virtually absent with intrathecal administration of morphine.

INDICATION AND USAGE

INFUMORPH™ (Preservative-free Morphine Sulfate Sterile Solution) is indicated only for intrathecal or epidural infusion in the treatment of intractable chronic pain. It was developed for use in continuous microinfusion devices and may require dilution before use as dictated by the characteristics of the device and the dosage requirements of the individual patient.

INFUMORPH™ IS NOT RECOMMENDED FOR SINGLE-DOSE INTRAVENOUS, INTRAMUSCULAR OR SUBCUTANEOUS ADMINISTRATION DUE TO THE VERY LARGE AMOUNT OF MORPHINE IN THE AMPUL AND THE ASSOCIATED RISK OF OVERDOSAGE.

CONTRAINDICATIONS

The only absolute contraindication to the use of INFUMORPH™ is known allergy to morphine. Contraindications to the use of neuraxial analgesia include: the presence of infection at the injection microinfusion site, concomitant anti-coagulant therapy, uncontrolled bleeding diathesis and the presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous.

WARNINGS

THIS PRODUCT WAS DEVELOPED FOR USE (AFTER APPROPRIATE DILUTION, IF NECESSARY) IN CONTINUOUS MICROINFUSION DEVICES FOR INTRATHECAL OR EPIDURAL INFUSION OF NARCOTICS TO CONTROL SEVERE CANCER PAIN. CHRONIC NEURAXIAL OPIOID ANALGESIA IS APPROPRIATE ONLY WHEN LESS INVASIVE MEANS OF CONTROLLING PAIN HAVE FAILED AND SHOULD ONLY BE UNDERTAKEN BY THOSE WHO ARE EXPERIENCED IN APPLYING THIS TREATMENT IN A SETTING WHERE ITS COMPLICATIONS CAN BE ADEQUATELY MANAGED.

BECAUSE OF THE RISK OF SEVERE ADVERSE EFFECTS, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS AFTER THE INITIAL (SINGLE) TEST DOSE AND, AS APPROPRIATE, FOR THE FIRST SEVERAL DAYS AFTER CATHETER IMPLANTATION.

THE FACILITY MUST BE EQUIPPED TO RESUSCITATE PATIENTS WITH SEVERE OPIATE OVERDOSAGE, AND THE PERSONNEL MUST BE FAMILIAR WITH THE USE AND LIMITATIONS OF SPECIFIC NARCOTIC ANTAGONISTS (NALOXONE, NALTREXONE) IN SUCH CASES.

RESERVOIR FILLING MUST BE PERFORMED BY FULLY TRAINED AND QUALIFIED PERSONNEL, FOLLOWING THE DIRECTIONS PROVIDED BY THE DEVICE MANUFACTURER. CARE SHOULD BE TAKEN IN SELECTING THE PROPER REFILL FREQUENCY TO PREVENT DEPLETION OF THE RESERVOIR, WHICH WOULD RESULT IN EXACERBATION OF SEVERE PAIN AND/OR REFLUX OF CSF INTO SOME DEVICES. STRICT ASEPTIC TECHNIQUE IN FILLING IS REQUIRED TO AVOID BACTERIAL CONTAMINATION AND SERIOUS INFECTION. **EXTREME CARE MUST BE TAKEN TO ENSURE THAT THE NEEDLE IS PROPERLY IN THE FILLING PORT OF THE DEVICE BEFORE ATTEMPTING TO REFILL THE RESERVOIR. INJECTING THE SOLUTION INTO THE TISSUE AROUND THE DEVICE OR (IN THE CASE OF DEVICES THAT HAVE MORE THAN ONE PORT) ATTEMPTING TO INJECT THE REFILL DOSE INTO THE DIRECT INJECTION PORT WILL RESULT IN A LARGE, CLINICALLY SIGNIFICANT, OVERDOSAGE TO THE PATIENT.**

A PERIOD OF OBSERVATION APPROPRIATE TO THE CLINICAL SITUATION SHOULD FOLLOW EACH REFILL OR MANIPULATION OF THE DRUG RESERVOIR. BEFORE DISCHARGE, THE PATIENT AND ATTENDANT(S) SHOULD RECEIVE INSTRUCTION IN THE PROPER HOME CARE OF THE DEVICE AND INSERTION SITE AND IN THE RECOGNITION AND PRACTICAL TREATMENT OF AN OVERDOSE OF NEURAXIAL MORPHINE.

TOLERANCE AND MYOCLONIC ACTIVITY

PATIENTS SOMETIMES MANIFEST UNUSUAL ACCELERATION OF NEURAXIAL MORPHINE REQUIREMENTS, WHICH MAY CAUSE CONCERN REGARDING SYSTEMIC ABSORPTION AND THE HAZARDS OF LARGE DOSES; THESE PATIENTS MAY BENEFIT FROM HOSPITALIZATION AND DETOXIFICATION. TWO CASES OF MYOCLONIC-LIKE SPASM OF THE LOWER EXTREMITIES HAVE BEEN REPORTED IN PATIENTS RECEIVING MORE THAN 20 MG/DAY OF INTRATHECAL MORPHINE AFTER DETOXIFICATION. IT MIGHT BE POSSIBLE TO RESUME TREATMENT AT LOWER DOSES, AND SOME PATIENTS HAVE BEEN SUCCESSFULLY CHANGED FROM CONTINUOUS EPIDURAL MORPHINE TO CONTINUOUS INTRATHECAL MORPHINE. REPEAT DETOXIFICATION MAY BE INDICATED AT A LATER DATE. THE UPPER DAILY DOSAGE LIMIT FOR EACH PATIENT DURING CONTINUING TREATMENT MUST BE INDIVIDUALIZED.

PRECAUTIONS

Control of pain by neuraxial opiate delivery, using a continuous microinfusion device, is always accompanied by considerable risk to the patients and requires a high level of skill to be successfully accomplished. The task of treating these patients must be undertaken by experienced clinical teams, well-versed in patient selection, evolving technology and emerging standards of care. For reasons of safety, it is recommended that administration of INFUMORPH™ 200 and 500 (10 and 25 mg/mL, respectively) by the intrathecal route be limited to the lumbar area.

USE IN PATIENTS WITH INCREASED INTRACRANIAL PRESSURE OR HEAD INJURY

INFUMORPH™ (Preservative-free Morphine Sulfate Sterile Solution) should be used with extreme caution in patients with head injury or increased intracranial pressure. Pupillary changes (miosis) from morphine may obscure the existence, extent and course of intracranial pathology. High doses of neuraxial morphine may produce myoclonic events (see WARNINGS and ADVERSE REACTIONS). Clinicians should maintain a high index of suspicion for adverse drug reactions when evaluating altered mental status or movement abnormalities in patients receiving this modality of treatment.

USE IN CHRONIC PULMONARY DISEASE

Care is urged in using this drug in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis or paralysis of the phrenic nerve). INFUMORPH™ should not be given in cases of chronic asthma, upper airway obstruction or in any other chronic pulmonary disorder without due consideration of the known risk of acute respiratory failure following morphine administration in such patients.

USE IN HEPATIC OR RENAL DISEASE

The elimination half-life of morphine may be prolonged in patients with reduced metabolic rates and with hepatic and/or renal dysfunction. Hence, care should be exercised in administering INFUMORPH™ epidurally to patients with these conditions, since high blood morphine levels, due to reduced clearance, may take several days to develop.

USE IN BILIARY SURGERY OR DISORDERS OF THE BILIARY TRACT

As significant morphine is released into the systemic circulation from neuraxial administration, the ensuing smooth muscle hypertonicity may result in biliary colic.

USE WITH DISORDERS OF THE URINARY SYSTEM

Initiation of neuraxial opiate analgesia is frequently associated with disturbances of micturition, especially in males with prostatic enlargement. Early recognition of difficulty in urination and prompt intervention in cases of urinary retention is indicated.

USE IN AMBULATORY PATIENTS

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be monitored for the possible occurrence of orthostatic hypotension, a frequent complication in single-dose neuraxial morphine analgesia.

USE WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

The depressant effects of morphine are potentiated by the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs. Use of neuroleptics in conjunction with neuraxial morphine may increase the risk of respiratory depression.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Morphine is without known carcinogenic or mutagenic effects and is not known to impair fertility at non-narcotic doses in animals, but studies of the carcinogenic and mutagenic potential or the effect on fertility of INFUMORPH™ have not been conducted.

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PREGNANCY CATEGORY C

Morphine sulfate is not teratogenic in rats at 35 mg/kg/day (thirty-five times the usual human dose) but does result in increased pup mortality and growth retardation at doses that narcotize the animal (>10 mg/kg/day, ten times the usual human dose). INFUMORPH™ should only be given to pregnant women when no other method of controlling pain is available and means are at hand to manage the delivery and perinatal care of the opiate-dependent infant.

LABOR AND DELIVERY

INFUMORPH™ 200 and 500 (10 and 25 mg/mL, respectively) are too highly concentrated for routine use in obstetric neuraxial analgesia.

NURSING MOTHERS

Morphine is excreted in maternal milk. Effects on the nursing infant are not known.

PEDIATRIC USE

Adequate studies, to establish the safety and effectiveness of spinal morphine in children, have not been performed, and usage in this population is not recommended.

USE IN THE AGED

The pharmacodynamic effects of neuraxial morphine in the aged are more variable than in the younger population. Patients will vary widely in the effective initial dose, rate of development of tolerance and the frequency and magnitude of associated adverse effects as the dose is increased. Initial doses should be based on careful clinical observation following "test doses", after making due allowances for the effects of the patient's age and infirmity on their ability to clear the drug, particularly in patients receiving epidural morphine.

ADVERSE REACTIONS

IMPROPER OR ERRONEOUS SUBSTITUTION OF INFUMORPH™ 200 or 500 (10 or 25 mg/mL, respectively) FOR REGULAR DURAMORPH® (0.5 or 1 mg/mL) IS LIKELY TO RESULT IN SERIOUS OVERDOSAGE, LEADING TO SEIZURES, RESPIRATORY DEPRESSION AND, POSSIBLY, FATAL OUTCOME.

The most serious adverse experiences encountered during continuous intrathecal or epidural infusion of INFUMORPH™ are respiratory depression and myoclonus.

1. Single-dose neuraxial administration may result in acute or delayed respiratory depression for periods at least as long as 24 hours. **Severe respiratory depression, potentially life-threatening, can result from technical errors during refill, e.g., injection of INFUMORPH™ outside the filling port, unintentional injection into the direct bypass-dosing port featured on some devices or local infiltration.**
2. **Tolerance and myoclonus:** See **WARNINGS** for discussion of these and related hazards.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from **sympathetic hyperactivity** and increase in circulating catecholamines. Excitation of the central nervous system, resulting in **convulsions**, may accompany high doses of morphine given intravenously. **Dysphoric reactions** may occur after any size dose and **toxic psychoses** have been reported.

Pruritus: Single-dose epidural or intrathecal administration is accompanied by a high incidence of **pruritus** that is dose-related but not confined to the site of administration. Pruritus, following continuous infusion of epidural or intrathecal morphine, is occasionally reported in the literature; these reactions are poorly understood as to their cause.

Urinary retention: Urinary retention, which may persist 10 to 20 hours following single epidural or intrathecal administration, is a frequent side effect and must be anticipated primarily in male patients, with a somewhat lower incidence in females. Also frequently reported in the literature is the occurrence of urinary retention during the first several days of hospitalization for the initiation of continuous intrathecal or epidural morphine therapy. Patients who develop urinary retention have responded to cholinomimetic treatment and/or judicious use of catheters (see PRECAUTIONS).

Constipation: Constipation is frequently encountered during continuous infusion of morphine; this can usually be managed by conventional therapy.

Headache: Lumbar puncture-type headache is encountered in a significant minority of cases for several days following intrathecal catheter implantation; this, generally, responds to bed rest and/or other conventional therapy.

Peripheral edema: There are several reports of peripheral edema, including unexplained genital swelling in male patients, following infusion-device implant surgery.

Other: Other adverse experiences reported following morphine therapy include—**Dizziness, euphoria, anxiety, depression of cough reflex, interference with thermal regulation** and **oliguria**. Evidence of histamine release such **as urticaria, wheals** and/or **local tissue irritation** may occur.

Pruritus, nausea/vomiting and urinary retention, if associated with continuous infusion therapy, may respond to intravenous administration of a low dose of naloxone (0.2 mg). The risks of using narcotic antagonists in patients chronically receiving narcotic therapy should be considered.

NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR USE IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS AND WHENEVER INFUMORPH™ THERAPY IS BEING INITIATED, THE RESERVOIR IS BEING REFILLED OR ANY MANIPULATION OF THE RESERVOIR SYSTEM IS TAKING PLACE.

DRUG ABUSE AND DEPENDENCE

CONTROLLED SUBSTANCE

Morphine sulfate is a Schedule II narcotic under the United States Controlled Substance Act (21 U.S.C. 801-886).

Morphine is the most commonly cited prototype for narcotic substances that possess an addiction-forming or addiction-sustaining liability. A patient may be at risk for developing a dependence to morphine if used improperly or for overly long periods of time. As with all potent opioids which are μ-agonists, tolerance as well as psychological and physical dependence to morphine may develop irrespective of the route of administration (intravenous, intramuscular, intrathecal, epidural or oral). Individuals with a prior history of opioid or other substance abuse or dependence, being more apt to respond to the euphorogenic and reinforcing properties of morphine, would be considered to be at greater risk.

Care must be taken to avert withdrawal in patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal symptoms may occur when morphine is discontinued abruptly or upon administration of a narcotic antagonist.

OVERDOSAGE

PARENTERAL ADMINISTRATION OF NARCOTICS IN PATIENTS RECEIVING EPIDURAL OR INTRATHECAL MORPHINE MAY RESULT IN OVERDOSAGE.

Overdosage of morphine is characterized by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center, or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted, or controlled, ventilation. The narcotic antagonist, naloxone, is a specific antidote. An initial dose of 0.4 to 2 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2- to 3-minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of narcotic-induced, or partial narcotic-induced, toxicity should be questioned. Intramuscular or subcutaneous administration may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization.

DOSAGE AND ADMINISTRATION

INFUMORPH™ 200 AND 500 (10 AND 25 MG/ML, RESPECTIVELY) SHOULD NOT BE USED FOR SINGLE-DOSE NEURAXIAL INJECTION BECAUSE LOWER DOSES CAN BE MORE RELIABLY ADMINISTERED WITH THE STANDARD PREPARATION OF DURAMORPH® (0.5 AND 1 MG/ML).

CANDIDATES FOR NEURAXIAL ADMINISTRATION OF INFUMORPH™ IN A CONTINUOUS MICROINFUSION DEVICE SHOULD BE HOSPITALIZED TO PROVIDE FOR ADEQUATE PATIENT MONITORING DURING

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ASSESSMENT OF RESPONSE TO SINGLE DOSES OF INTRATHECAL OR EPIDURAL MORPHINE. HOSPITALIZATION SHOULD BE MAINTAINED FOR SEVERAL DAYS AFTER SURGERY INVOLVING THE INFUSION DEVICE FOR ADDITIONAL MONITORING AND ADJUSTMENT OF DAILY DOSAGE. THE FACILITY MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION AND OTHER RESUSCITATIVE DRUGS. BECAUSE OF THE RISK OF DELAYED RESPIRATORY DEPRESSION, PATIENTS SHOULD BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS AFTER EACH TEST DOSE AND, AS INDICATED, FOR THE FIRST SEVERAL DAYS AFTER SURGERY.

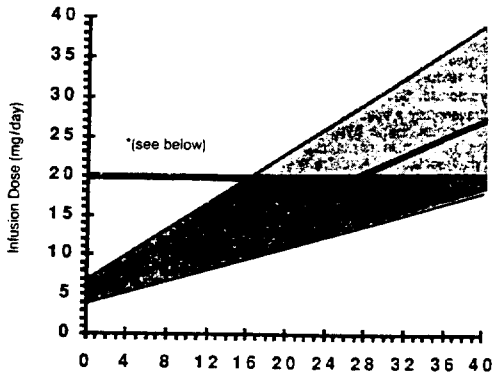
Familiarization with the continuous microinfusion device is essential. The desired amount of morphine should be withdrawn from the ampul through a microfilter. **To minimize risk from glass or other particles, the product must be filtered through a 5 μ (or smaller) microfilter before injecting into the microinfusion device.** If dilution is required, 0.9% Sodium Chloride Injection is recommended.

Intrathecal Dosage: The starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose intrathecal bolus injections of regular DURAMORPH® 0.5 mg/mL or 1 mg/mL, with close observation of the analgesic efficacy and adverse effects *prior* to surgery involving the continous microinfusion device.

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1 mg/day. The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10 mg/day. The upper daily dosage limit for each patient must be individualized.

Limited experience with continuous intrathecal infusion of morphine has shown that the daily doses have to be increased over time. Although the rate of increase, over time, in the dose required to sustain analgesia is highly variable, an estimate of the expected rate of increase is shown in the following Figure.

Figure: Dose Trend in Continuous Infusions of Intrathecal Morphine (Mean and 95% Confidence Intervals)



*20 mg/day is the lowest dose for which regional myoclonus has been reported. The rate of occurrence cannot be estimated.

Doses above 20 mg/day should be employed with caution since they may be associated with a higher likelihood of serious side effects (see WARNINGS concerning potential neurological hazards and ADVERSE REACTIONS).

Epidural Dosage: The starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural bolus injections of regular DURAMORPH® (Morphine Sulfate Injection, USP) 0.5 mg/mL or 1 mg/mL, with dose observation for analgesic efficacy and adverse effects *prior* to surgery involving the continuous microinfusion device.

The recommended initial epidural dose in patients who are not tolerant to opioids ranges from 3.5 to 7.5 mg/day. The usual starting dose for continuous epidural infusion, based upon limited data in patients who have some degree of opioid tolerance, is 4.5 to 10 mg/day. The dose requirements may increase significantly during treatment, frequently to 20-30 mg/day. The upper daily limit for each patient must be individualized.

SAFETY AND HANDLING INSTRUCTIONS

INFUMORPH™ is supplied in sealed ampuls. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

Each ampul of INFUMORPH™ contains a large amount of a potent narcotic which has been associated with abuse and dependence among health care providers. **Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic. *INFUMORPH™ should be subject to rigid accounting, rigorous control of wastage and restricted access.***

This parenteral drug product must be inspected for particulate matter before opening the amber ampul and again for color after removing contents from the ampul. Do not use if the solution in the unopened ampul contains a precipitate which does not disappear upon shaking. After removal, do not use unless the solution is colorless or pale yellow.

HOW SUPPLIED

Amber **DOSETTE®** ampuls for epidural or intrathecal administration via a continuous microinfusion device.

INFUMORPH™ 200 (Preservative-free Morphine Sulfate Sterile Solution)
200 mg/20 mL (10 mg/mL) packaged individually (*NDC* 0641-1131-31)

INFUMORPH™ 500 (Preservative-free Morphine Sulfate Sterile Solution)
500 mg/20 mL (25 mg/mL) packaged individually (*NDC* 0641-1132-31)

Also available from Elkins-Sinn, Inc.: DURAMORPH® (Morphine Sulfate Injection, USP) 5 mg/10 mL (0.5 mg/mL) and 10 mg/10 mL (1 mg/mL). See insert J-1113.

STORAGE

Protect from light. Store in carton at controlled room temperature 15°-30°C (59°-86°F) until ready to use. DO NOT FREEZE. INFUMORPH™ contains no preservative or antioxidant. DISCARD ANY UNUSED PORTION. DO NOT HEAT-STERILIZE.

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Additional package inserts may be obtained by contacting the Professional Services Department.

Issued February 1991
J-1131a

Manufactured by
ELKINS-SINN, INC. Cherry Hill, NJ 08003-4099
A subsidiary of A.H. Robins Company

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Appendix

APPENDIX 2

Statement by
Timothy A. Ulatowski
Chief, General Hospital Devices Branch

3/5/91

MORNING PRESENTATION

Before the morning presentation to the panel begins, I'd like to give a brief overview of FDA's perspective regarding the evaluation of implantable infusion pumps. I will supplement this overview with brief introductory remarks prior to the next presentation.

Drug delivery products, such as infusion pumps, ports, IV sets, catheters, and syringes that are not sold pre-filled with a drug are currently regulated as medical devices. The device product approvals are administered by the Center for Devices and Radiological Health. Drugs that are delivered by these devices are currently regulated and approvals administered by the Center for Drug Evaluation and Research. The drug and device together provide a safe and effective therapeutic or diagnostic tool when used in accordance with their labeling.

Although drugs and drug delivery devices are regulated by separate FDA components, the determination of the safety and effectiveness of both are interrelated. The precise determination of the safety and effectiveness of the drug depends in part upon the performance and reliability of the specific delivery system that is used. The safety and effectiveness of the delivery system depends in part on the compatibility of the device with the drug and on the drug's dosage and administration requirements. In terms of the complexity

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of product approval, we are faced with new drugs to be used with marketed devices, new devices to be used with marketed drugs, or new drugs used with new devices, and many other situations. Since there is congruent authority, the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research consult on scientific matters related to drug and device combinations. Recent changes in FDA's statutory authority allow FDA to take steps to simplify the regulatory process.

Now that I've illustrated the complex regulatory environment in which are operating I want to clarify, and define the scope of the task before the panel.

You are asked to decide whether the premarket approval applications...PMAs...for the infusion pumps you will consider today provide reasonable assurance that the devices are safe and effective for their intended use. The intended use of an infusion pump, simply stated, is to deliver an approved drug for the intended use, by the route of administration, and the dosage defined in the approved drug labeling. We are NOT here today to determine the safety and effectiveness of any drug. The safety and effectiveness of the drugs encountered today have been, or soon will be, established.

How do drugs mesh with pumps in a regulatory sense? FDA approvals for <u>most</u> EXTERNAL infusion pumps are independent of specific drugs.

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Some external pumps are dedicated to a specific drug. On the other hand, specific drugs and the drug labeling must be always be considered for implantables. Still, even with implantables there is flexibility. Generally, once an implantable pump is clinically qualified for a particular route of administration, additional drugs for the same route of administration can be added to the pump labeling without clinical data. Manufacturers must submit drug and device stability and compatibility data and the labeling for the drug and device must otherwise be compatible. In essence, one does not have to reprove the fundamental safety and effectiveness of the pump.

The determination of the effectiveness of an implantable pump is based upon the data contained in the PMA including in vitro and in vivo data documenting the performance and reliability of the pump and catheter. One indicator of effectiveness is the deviation of the actual drug flow from that expected. A second indicator is the progress of the patient which demonstrates that the drug was actually delivered to the site in the desired manner. Significant deviations in flow or inability to deliver the drug to the site are cause for concern and it must be determined whether anomalies are device failures.

The determination of safety is based upon the same data. The sponsor must identify all complications and segregate them such that the device and technique related adverse effects and their

causation can be distinguished from drug effects or other effects unrelated to the implant. Device related adverse effects should be within acceptable limits.

In sum, the known risks of the implantable pump must be weighed against its demonstrated benefits.

The options to consider for the first device, DEVICE A, are as follows:

1. The panel believes that based upon the data presented to them in the application and upon the discussion there is reasonable assurance that DEVICE A is safe and effective for the delivery of FUDR and therefore should be approved. There are no deficiencies in the application identified by the panel nor are there other panel concerns that must be resolved before or after approval.

   OR

2. The panel believes that based upon the data presented to them in the application and upon the discussion there is reasonable assurance that DEVICE A is safe and effective for the delivery of FUDR and therefore should be approved. However, there are deficiencies or concerns regarding the safety and

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effectiveness of DEVICE A that remain. These questions or concerns must be specified. The questions or concerns are such that DEVICE A can be approved once the conditions are met or they can be answered in a post approval format.

OR

3. The panel believes that based upon the data presented to them in the application and upon the discussion there is not reasonable assurance that DEVICE A is safe and effective for the delivery of FUDR and therefore should not be approved. This choice will be discussed in further detail before the vote. The deficiencies in the application must be specified.

AFTERNOON PRESENTATION

You are now going to consider the second implantable infusion pump. In this case there are two drugs that are indicated for use, FUDR and preservative free morphine sulfate. We have already considered FUDR which I will not discuss further. Let me provide some background from FDA's perspective on the use of morphine sulfate with implantable pumps, and once again define the scope of the discussion.

Duramorph or Astramorph, generically known as preservative free morphine sulfate injection, USP, supplied in .5mg/ml and 1mg/ml concentrations, are the only morphines currently approved for intrathecal and epidural administration. Because of their relatively low concentration, they have **very** limited utility for implantable pumps because of the higher dosage requirements for many patients. The need for a more concentrated approved form of preservative free morphine that can provide physicians the desired dosage flexibility was identified almost a decade ago. Efforts to provide such a high concentrate preservative free morphine approved for use in infusion pumps are hopefully going to be successful in the near future.

How do physicians manage patients without an approved high concentrate morphine? In the interim, lacking an approved high concentrate morphine, individual physicians and those taking part

in clinical studies evaluating pain management with implantable infusion pumps have used pharmacy formulated morphine to achieve the concentrations necessary for effective pain management. A limited supply of a preservative free high concentrate morphine has also been available from a pharmaceutical firm for investigational use only.

FDA will **NOT** approve a drug delivery device for which there is no compatible approved drug. Likewise, we strive not to approve a PMA for a device for a mode of use of a drug that is contrary to the drug labeling. Approval of Duramorph provided FDA the first opportunity to approve implantable infusion pumps for at least an epidural route of administration. The dosage section of Duramorph describes epidural administration by "continuous infusion." Only one manufacturer currently has an approved PMA for implanted infusion pumps for epidural administration of approved preservative free morphine. As noted, we recognize that Duramorph does not provide the flexibility needed by the physician, and epidural administration is now a small segment of current usage, but the approval of implantable pumps for epidural use was at least a step forward.

The intended use for the implanted pumps approved for epidural administration indicates epidural delivery of preservative free morphine for intractable pain of malignant origin. The intended use of Duramorph reads "the management of <u>pain</u> not responsive to

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non-narcotic analgesics." Note that the pain etiology is not defined. Much of the clinical data supporting the approved drug is based on post-op or obstetrical pain. Obviously, from a risk/benefit point of view one should not implant a pump to deal with an acute situation. One should not implant a pump for a condition that is responsive to a therapy with a better risk/benefit ratio. Therefore, intractability of pain, and pain of maliganant origin were valid limiters for the implanted pump.

To reiterate, the implantable infusion pump is intended simply to infuse a drug. It is the drug labeling that defines the use of the drug. The pump must be capable of providing the drug as the drug labeling directs. We are **NOT** here to determine the safety and effectiveness of any drug.

A higher concentration of preservative free morphine is pending approval. We in this Center cannot state with absolute certainty what will be its labeled intended use. Still, we believe it is prudent to anticipate labeling for a high concentrate morphine that is intended for treatment of intractable pain...of malignant or benign origin. This will be the thrust of a portion of the presentation to take place.

The morphine data in the PMA sent to you for evaluation include pain of both malignant **AND** benign origin. This was not apparent to FDA based on the information included in the PMA. Nevertheless,

the manufacturer will clarify the data for us today and in a follow-up submission for FDA evaluation. Although this is news to you and complicates matters, we believe you can reasonably adjust to the situation.

What are the implications of the drug indication, as defined, for the device? Long-term reliability for treatment of chronic benign pain must be considered. This was less of a concern from a risk/benefit angle for malignant pain. All relevant aspects of catheter placement must be considered. Recognizing the current predominance of intrathecal administration of morphine and paucity of epidural implants, and the relatively greater risk of intrathecal use compared to epidural use, is it clinically sound from a device perspective to forego the need for epidural implants to support an epidural claim if there are sufficient intrathecal cases? In other words, can we extrapolate device experience on intrathecal implants to an epidural claim for a pump?

The decision options previously mentioned for DEVICE A are the same when considering use of the DEVICE B for administration of FUDR and morphine. Since DEVICE B is indicated for two drugs there are more alternatives that can be considered by the panel. We will address these matters further at the end of the session, as necessary.

The deliberations of the panel are precedent setting in this issue. Others may be affected so we wish the record to be as definitive

as possible.

Appendix 3

APPENDIX 3

One Place Your Text Could Go (See Documentation Section 6)

REFERENCES

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Appendix

APPENDIX 4

Medtronic SynchroMed®
Infusion System

SYSTEM DESCRIPTION

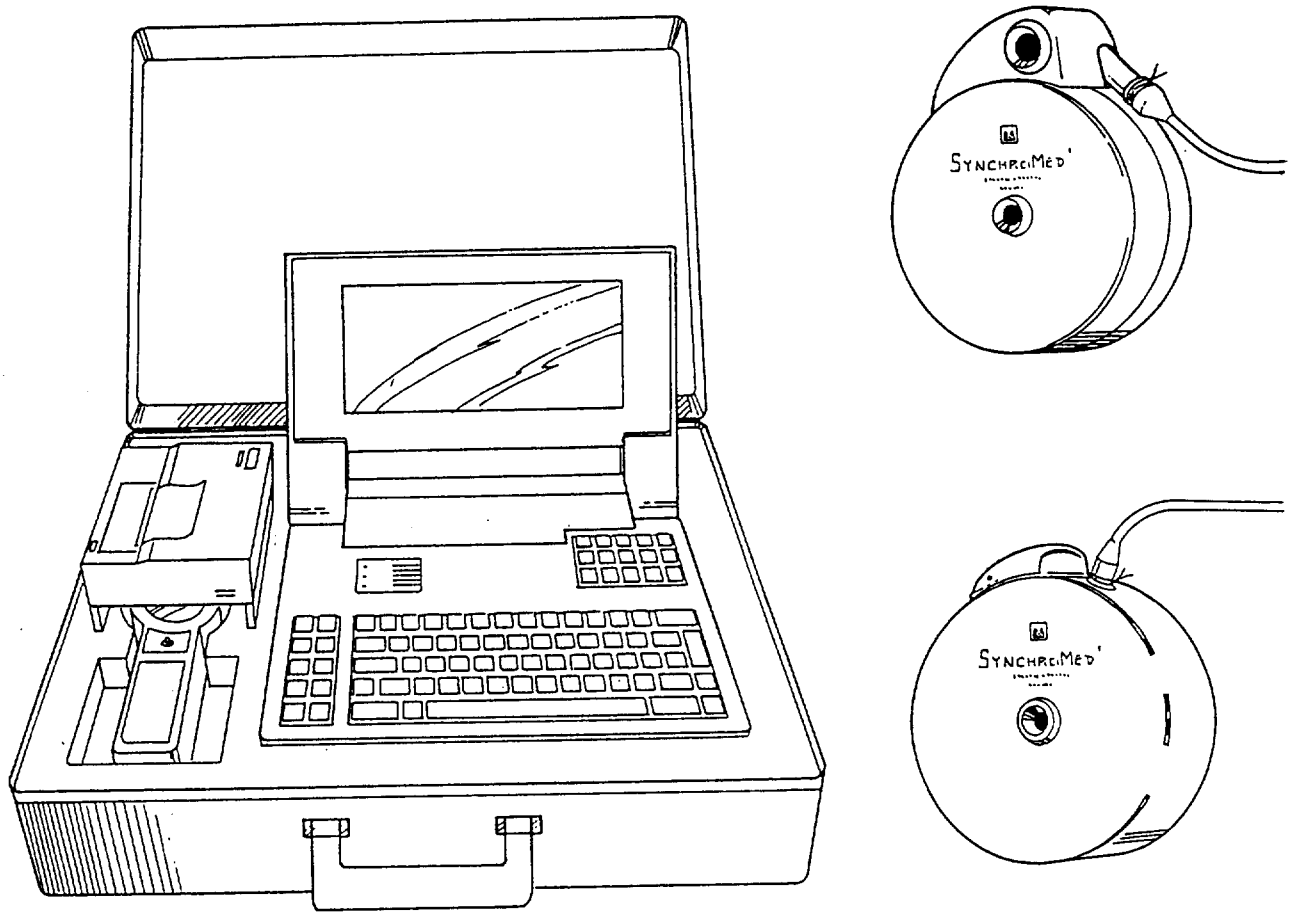
CAUTION: Federal law (USA) restricts this device to sale, distribution, and use by or on the order of a physician. This device is approved for chronic intravascular infusion of floxuridine, doxorubicin, heparin, cisplatin, methotrexate, clindamycin, and intraspinal infusion of preservative-free morphine sulfate. **ALL OTHER USES ARE CONSIDERED INVESTIGATIONAL.**

Medtronic and SynchroMed are trademarks of Medtronic, Inc.

CONTENTS

PREFACE

The Medtronic SynchroMed® Infusion System includes a programmable pump, a programmer, a catheter access system, catheters, and accessories.



SynchroMed Infusion System

The system is designed to contain and to administer parenteral drugs to a specific site. The implantable devices include the pump, catheter access system, catheters, and accessories. The external part of the system is the SynchroMed Model 8810 Programmer, which is used to noninvasively program and interrogate the implanted pump.

INDICATIONS

The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intravascular infusion of floxuridine or doxorubicin. In addition, the nontherapeutic use of bacteriostatic water, physiological saline, and/or heparin is indicated when necessary to support this mode of cancer therapy.

The regional intra-arterial infusion of floxuridine is used in the palliative management of unresectable solid colorectal tumors metastatic to the liver.

The systemic intravenous infusion of doxorubicin is used in the palliative management of various solid tumors, lymphomas, and leukemias.

When patient therapy requires the chronic intraspinal (epidural/intrathecal) infusion of preservative-free morphine sulfate sterile solution (10 mg/mL and 25 mg/mL) in the treatment of chronic intractable pain (Models 8611H and 8615 only).

A 0.9% solution of preservative-free sodium chloride can be used to achieve the physician-prescribed concentration of preservative-free morphine sulfate sterile solution.

Bacteriostatic water or physiological saline can be used to achieve the physician-prescribed concentration of floxuridine or doxorubicin or to flush the pump reservoir. Heparinized physiological saline may be used during an interruption in floxuridine therapy to maintain catheter patency.

Physicians prescribing the SynchroMed Infusion System for use with floxuridine, doxorubicin, or preservative-free morphine sulfate sterile solution must be familiar with the indications, contraindications, and warnings described in the drug labeling. Except under approved conditions of Investigational Device Exemptions, the use of the SynchroMed Infusion System is restricted to the infusion of the drugs and fluids previously described.

CONTRAINDICATIONS

The device should not be implanted in the presence of infection.

Implantation is contraindicated when the pump cannot be implanted less than 2.5 cm (one inch) from the surface of the skin and/or when the patient has an implanted programmable medical device.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable candidates.

Contraindications relating to the use of the prescribed drug should be observed.

SYSTEM DESCRIPTIONS

For a complete description of components, indications, contraindications, warnings, and precautions please refer to the appropriate sections of each component manual.

PROGRAMMABLE PUMPS

SynchroMed Models 8610H, 8611H, and 8615 Programmable Pumps are implantable, battery-powered devices that store and dispense drugs according to instructions received from the SynchroMed Programmer.

The pumps contain a collapsible 18 mL drug reservoir, microprocessor-based circuitry, lithium thionyl-chloride battery, antenna, acoustic transducer, peristaltic pump, and fill port with a self-sealing septum and a needle stop. Models 8611H and 8615 also contain a bacterial retentive filter through which the drug passes as it leaves the drug reservoir. Model 8615 incorporates an integral Catheter Access Port with the pump to allow direct access to the catheter.

The pump has three sealed chambers: One contains the drug reservoir, the second a hybrid electronic module and battery, and the third a peristaltic pump. The peristaltic pump forces the drug from the reservoir through elastomeric tubing into a catheter to the administration site. Electronic circuitry controls the pumping action.

The Catheter Access Port provides a transcutaneous entry point, via syringe, to an implanted catheter for drug administration and diagnostic purposes. The system allows one catheter to deliver infusions from both a SynchroMed Pump and an access port. The access port comes integrally attached to the SynchroMed Pump.

The access port housing is made of biocompatible silicone rubber and titanium and contains a self-sealing septum, needle stop, infusion pathway, titanium catheter port, and an in-line valve. The in-line valve directs infusion flow from the access port toward the catheter infusion site and prevents fluid from passing back to the pump. When the pressure from the access port injection is removed, the infusion from the pump continues into the catheter.

Before the pump is sealed in the plastic tray and sterilized, its 18 mL drug reservoir is filled with 14-16 mL of sterile water for injection. The titanium drug reservoir is emptied and refilled through the self-sealing silicone septum in the raised fill port.

A Dacron pouch included in the pump package serves to fix the pump in the subcutaneous pocket (all pump models) as well as to anchor the optional catheter access system (Models 8610H and 8611H).

Examine the shipping package carefully. If the package is damaged or the "Use Before..." date is past, do not implant or resterilize the pump. Return the pump and its shipping package to Medtronic, Inc.

To assure SynchroMed pump accuracy: limit the reservoir fill volume at implant to 10 mL and subsequent refill volumes to 18 mL. Program the pump to deliver not less than 0.096 mL/day (0.004 mL/hour).

The following programmable modes have not been used in cancer chemotherapy clinical studies: bolus and bolus delay. These modes are not recommended for vascular applications due to the intermittent periods of no flow and the possible increased risk of catheter occlusion.

VASCULAR CATHETERS

SynchroMed Vascular Catheters are totally implantable devices designed to provide a fluid pathway for drug administration and/or diagnostic procedures. The catheter body is constructed of radiopaque

materials and incorporates a strain-relief connector assembly for attachment to a SynchroMed Programmable Pump or Medtronic Catheter Access Port.

The Model 8700 Vascular Catheter is designed for general intravascular use and may be trimmed to desired length. Fixation rings are attached to the distal portion. The catheter comes packaged with a guidewire, anchoring sleeves, and plastic tips for a metal tunneling rod (supplied separately).

The Model 8702 Vascular Catheter is designed specifically for intra-arterial, small vessel access, and may be trimmed to facilitate introduction. Fixation rings are attached to the distal portion. The catheter is packaged with anchoring sleeves and plastic tips for a metal tunneling rod (supplied separately).

The Model 8710 Vascular Catheter is designed for intravenous use and cannot be trimmed to length because of its trilaminate construction (a small inner silicone tubing, a high-strength metal coil, and a large outer silicone tubing). Therefore, the Model 8710 is provided in two lengths. It is packaged with anchoring sleeves and plastic tips for a metal tunneling rod (supplied separately).

Catheter occlusions may inhibit drug delivery. Refer to the vascular catheters technical manual for details on methods of clearing an occluded catheter.

To maintain catheter patency during periods of nontherapy, the pump should be emptied of drug and filled with saline (or an appropriate heparinized solution) and programmed to a continuous flow rate of not less than 0.096 mL/day. Do not stop the pump during periods of nontherapy.

INTRASPINAL CATHETER (Model 8703)

SynchroMed intraspinal catheters are totally implantable and designed to provide a fluid pathway for drug administration. The catheter body is constructed of radiopaque materials and is elastic, flexible, and trimmable.

The Model 8703 Intraspinal Catheter is a two-piece device designed for epidural/intrathecal use. The pump connector on the proximal section of the catheter segment connects to the pump and relieves strain on the catheter. A metal connector assembly facilitates connection of the two catheter sections.

CATHETER ACCESS SYSTEM

The SynchroMed Model 8500-1 Catheter Access System provides a transcutaneous entry point, via syringe, to an implanted SynchroMed Catheter for drug administration and/or diagnostic purposes. The system allows a catheter to be attached to both a SynchroMed Pump and an access port.The access port housing is a molded biocompatible thermoplastic and contains a self-sealing septum, needle stop, infusion pathway, three suture points, and a titanium catheter port. The connector assembly is a T-shaped connector consisting of two silicone connectors, a titanium catheter port, and an in-line valve.

The catheter access system is not intended for use in blood withdrawal. If the presence of blood is suspected in the catheter access system, flush the system with a minimum of 10 mL of saline (a heparinized solution may be used if not contraindicated).

PROGRAMMER

The SynchroMed Model 8810 Programmer is designed for use by the clinician to noninvasively program and interrogate an implanted SynchroMed Programmable Pump. The programmer establishes a two-way, radio-frequency (RF) link with the implanted pump to transmit interrogation and programming signals to the pump and to receive status information from the pump. The programmer includes a computer, programming wand, and printer. The programmer is powered by a rechargeable battery pack. The Model 8810 SynchroMed Programmer should be used only for programming Medtronic SynchroMed Programmable Pumps. The programmer operates best in an environment which is free from strong electromagnetic interference.

TECHNICAL SUPPORT

A toll-free technical support service is available 24 hours a day for clinicians managing SynchroMed Infusion System implants: Telephone Customer Service at : 1-800-328-0810.

Medtronic

Medtronic Neurological
800 53rd Avenue NE
PO Box 1250
Minneapolis, MN 55440-9087 USA
(612) 572-5000
1-800-328-0810

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August 1991

Medtronic SynchroMed®
Infusion System
Model 8703 Intraspinal Catheter

TECHNICAL MANUAL

CONTENTS

CAUTION: Federal law (USA) restricts this device to sale, distribution, and use by or on the order of a physician. This device is approved for intraspinal infusion of preservative-free morphine sulfate. **ALL OTHER USES ARE CONSIDERED INVESTIGATIONAL.**

Medtronic and SynchroMed are trademarks of Medtronic, Inc.

SPECIFICATIONS

Catheter length	
Total	41.0 in. (104.1 cm)
Distal	15.0 in. (38.1 cm)
Proximal	26.0 in. (66.0 cm)
Outer diameter (distal)	0.049 in. (1.2 mm, 4 French)
Inner diameter (distal)	0.027 in. (0.7 mm)
Outer diameter (proximal)	0.085 in. (2.2 mm, 6.5 French)
Inner diameter (proximal)	0.025 in. (0.6 mm)
Catheter volume	8.08 ul/in. (3.18 ul/cm)
Catheter material	Radiopaque silicone rubber
Marker spacing	1 cm for 20 cm
Tubing connector material	Titanium
Inner diameter	0.025 in. (0.6 mm)
Strain relief sleeve material	Silicone rubber
Outer diameter (maximum)	0.360 in. (9.1 mm)
Guide wire outer diameter	0.018 in. (0.053 cm)
Percutaneous Introducer	16T-gauge epidural (Tuohy) needle

RESTERILIZATION

Do not resterilize the catheter and accessories after exposure to body tissues or fluids.

The catheter and accessories are sterilized by ethylene oxide prior to shipment. If the sealed plastic tray has been opened and the catheter and accessories have not been used, resterilize. Do not use radiation or flash autoclaving for resterilization.

Ethylene oxide is an acceptable method for resterilization when the catheter and accessories are repackaged in an ethylene oxide-permeable package. Allow adequate time for aeration before implanting the catheter and accessories.

Steam autoclaving may also be used as a resterilization method. A standard cycle of 30 minutes at 121°C (250°F) and 15 psi is recommended. Do not flash autoclave.

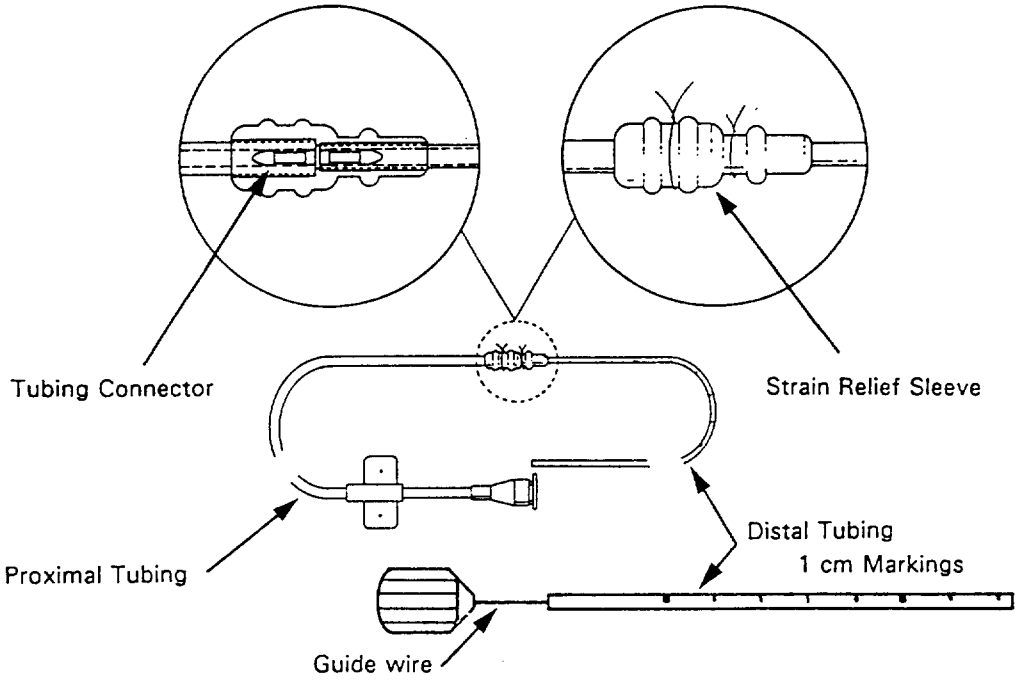
Due to variations among sterilizer units, precise sterilization instructions cannot be given here. However, the process should not exceed temperatures of 60°C (140°F). If further information is necessary regarding procedures to be used, contact the manufacturer of the sterilizer unit. Use biological indicators or another acceptable method to verify the effectiveness of the sterilizer unit.

DESCRIPTION

The catheter body sections (a distal thin-walled section and a proximal thicker-walled section) are made of radiopaque silicone rubber that is elastic, flexible and trimmable. The pump connector on the proximal section facilitates connection to the pump and relieves strain on the catheter segment near the pump connection. The metal connector assembly facilitates connection of the two catheter sections.

The distal section is marked at 1 cm increments for 20 cm to aid in catheter placement. It is packaged with a guide wire in the lumen to provide additional stiffness and catheter-tip control during placement.

The catheter may be used in the epidural or intrathecal space. The catheter can be positioned by direct percutaneous surgical procedures using the accessories provided in the catheter package.



SynchroMed Model 8703 Intraspinal Catheter

INDICATIONS

The Model 8703 Intraspinal Catheter is intended for use with the Medtronic SynchroMed® Infusion System. The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intraspinal infusion of preservative-free morphine sulfate sterile solution (10 mg/mL and 25 mg/mL) for the treatment of chronic intractable pain.

CONTRAINDICATIONS

Intraspinal catheterizations are contraindicated in the presence of known or suspected meningitis, ventriculitis, skin infection, bacteremia, and septicemia.

Spinal catheterization is contraindicated in the presence of spinal anomalies that may complicate the implantation and fixation of a lumbar catheter or drug delivery.

PRECAUTIONS

Examine the sealed plastic tray carefully. If the tray seal is broken, sterility is questionable. Resterilize the catheter and accessories with ethylene oxide. Do not sterilize with radiation or by flash autoclave.

Do not bend or kink the catheter and guide wire either before use or during implantation. The guide wire must be withdrawn before connecting the catheter sections together.

When reinserting the guide wire to verify or change catheter placement, no reinsertion force should be encountered. Excessive force could cut or puncture the catheter wall.

During implantation, verify that the catheter will not become kinked or occluded due to knots, tight geometries, or a tortuous position.

Sharp surgical instruments are capable of damaging catheter elastomers. Care must be taken to not inadvertently cut or puncture the catheter tubing.

Do not remove the connector attached to the proximal tubing section. Trim the distal tubing section only after placement is complete, guide wire is removed, and catheter is secured to tissue with an anchoring sleeve. DO NOT trim the distal section before placement or with guide wire in place.

POTENTIAL COMPLICATIONS

A clinical trial was performed to establish the safety and efficacy of the Medtronic SynchroMed Infusion System. Based upon the data collected during this clinical trial, the potential complications associated with the use of this device may include, but may not be limited to, the following: Cessation of therapy due to battery depletion or random component failure; pocket seroma, hematoma, erosion, or infection; catheter angulation; hygroma; and lumbar puncture-type headache.

INSTRUCTIONS FOR USE

Examine the sealed plastic tray carefully. If contamination is suspected for any reason, resterilize with ethylene oxide before implantation.

SPINAL CATHETERIZATION

The patient is placed in a lateral fetal position and draped to allow fluoroscopic visualization of the spine in the region where the catheter will be placed. Under local or regional epidural anesthesia, prepare a subcutaneous pocket to secure the pump to the abdominal wall. Consider pocket position to avoid locations which may interfere with patient mobility, clothing, belt lines, etc.

The catheter is most often placed in the lumbar epidural or intrathecal space using a 16-gauge Tuohy needle.

Epidural Placement

Orient bevel and insert 16-gauge epidural needle. Advance until tip is felt embedded in ligamentum flavum.

Remove needle stylet. To aid in determination of epidural space location, use hanging drop method or attach a 5 ml glass syringe to needle for loss of resistance technique.

Aspirate to ensure proper location of needle bevel in epidural space. Continue procedure if neither blood or CSF is obtained.

Thread distal tip of catheter (marked with cm graduations) through the epidural needle into the epidural space. A slight increase in advancement pressure will be noted when the tip of the catheter reaches the curved point of the epidural needle. The first cm graduation should now

approximately coincide with the end of the epidural needle hub. Subsequent pressure required to advance the catheter into the epidural space should be minimal.

Intrathecal Placement

Orient bevel and insert 16-gauge epidural needle. Under fluoroscopy, advance distal catheter segment to desired level.

To ensure catheter patency, withdraw the guide wire slightly to allow retrograde CSF flow until observed. Push the guide wire back in place and clamp the end of the distal tubing to the drape above the incision site ensuring stoppage of CSF flow.

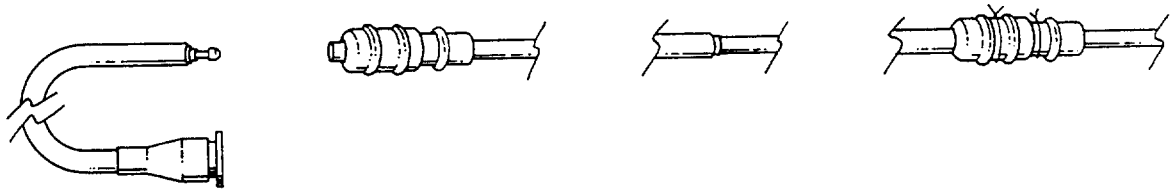
Following placement of the distal catheter segment, an incision is made at the spinal region so that the catheter can be secured subcutaneously (this incision can be made prior to catheter placement). Special care must be taken to not inadvertently cut or puncture the catheter during the procedure. To protect the catheter while the incision is being made, keep the Tuohy needle in place while the incision is made. Once the incision is complete, tissues are exposed for securing the catheter segment, and placement is confirmed, carefully remove the Tuohy needle, grasp catheter segment at incision point, and slowly withdraw guide wire.

For added stability, place an anchoring sleeve close to the spinal entry point and suture it to surrounding tissue.

Measure the length of proximal catheter tubing between pump and spinal region, allowing for slack in the catheter. Trim the segment if necessary, ensuring that the connector end is left intact. Unclamp and trim the distal tubing segment.

Refer to the figure and connect the distal catheter tubing to the proximal tubing as follows :

1. Insert metal tubing connector into proximal tubing (large diameter tubing with connector).
2. Slide strain relief sleeve (if used), small end first, over previously placed distal tubing.
3. Insert tubing connector into distal tubing using care not to disrupt catheter spinal placement.
4. Slide strain relief sleeve (if used) over connection and ligate. If the strain relief sleeve is not being used, ligate both sections of tubing as shown.



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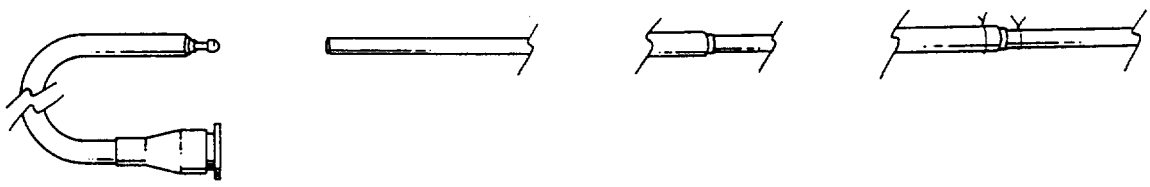
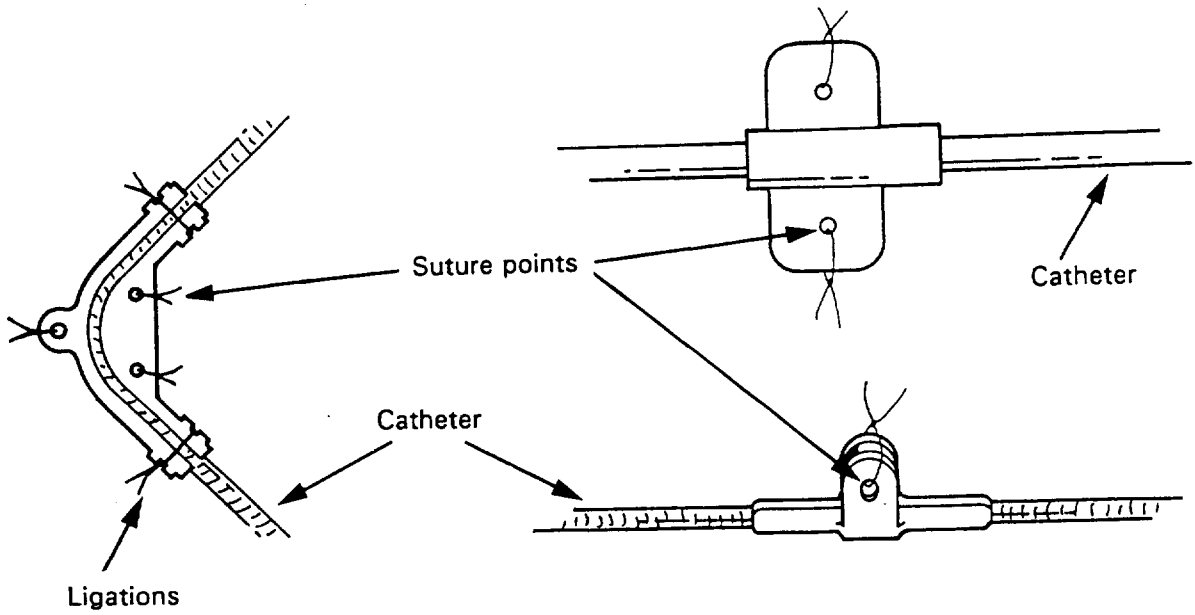
Connect Distal and Proximal Catheter Tubing (With Sleeve)



Connect Distal and Proximal Catheter Tubing (No Sleeve)

Place the catheter under the skin or tissue and pull toward the pump implant site with appropriate surgical tools, or by using the tunneling rod that is provided as an accessory (see "Catheter Tunneling").

Prevent excessive tension or angulation in the implanted catheter tubing. Use catheter anchoring sleeves to provide additional stability and to prevent unusual angulations that might kink the catheter tubing.



Anchoring sleeve placements

CATHETER TUNNELING

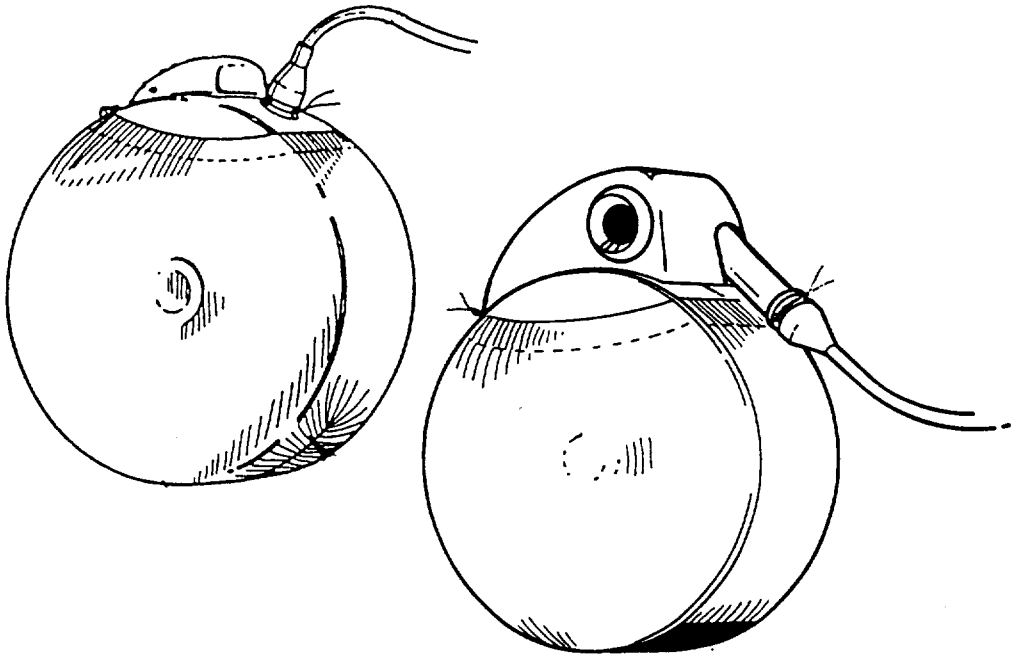
Reference instructions for tunneling procedure in Accessory Kit Model Number 8590-41.

CONNECTION TO PUMP

Before connecting the catheter to the pump, verify that the pump is functioning and set for the desired infusion parameters.

CAUTION: Do not inadvertently introduce air bubbles into the catheter.

Firmly press the silicone-rubber connector onto the tapered metal fitting of the pump and secure the connector with a nonabsorbable ligature placed in the suture groove at the base of the connector. Do not use chromium or wire sutures for ligation.



Push the connector onto the pump fitting and ligate

CAUTION: Do not inadvertently tear or puncture the catheter tubing with the metal pump fitting.

Place the pump in the incision (pocket) so that the catheter is not knotted or kinked, and so that the catheter tubing will not be punctured by needles used to refill the pump.

TECHNICAL SUPPORT

A toll-free technical support service is available 24 hours a day for clinicians managing SynchroMed Infusion System implants: Telephone Customer Service at: 1-800-328-0810.

DISCLAIMER OF WARRANTIES

MEDTRONIC SYNCHROMED® INFUSION SYSTEM
INTRASPINAL CATHETERS

WARNING:

Medtronic SynchroMed® Intraspinal Catheters (Catheters) are implanted in the extremely hostile environment of the human body. Catheters may fail to function for a variety of causes, including but not limited to, medical complications or failure of Catheters by complete or partial occlusion; breakage; dislodgement; or connector separation. In addition, despite the exercise of all due care in design, component selection, manufacture and testing prior to sale, Catheters may be easily damaged before, during, or after insertion by improper handling or other intervening acts. Consequently, no representation or warranty is made that failure or cessation of function of Catheters will not occur, that the body will not react adversely to the implantation of catheters, or that medical complications will not follow the implantation of catheters.

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Medtronic

Medtronic Neurological
800 53rd Avenue NE
PO Box 1250
Minneapolis, MN 55440-9087 USA
(612) 572-5000
(800) 328-0810

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Medtronic SynchroMed®
Infusion System
Preservative-Free Morphine Sulfate Sterile Solution

DRUG THERAPY SUPPLEMENT

CAUTION: Federal law (USA) restricts this device to sale, distribution, and use by or on the order of a physician.

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CONTENTS

INTRODUCTION

This supplement gives brief guidelines for the intraspinal infusion of preservative-free morphine sulfate sterile solution with the Medtronic SynchroMed® Model 8611H or 8615 Programmable Pump, part of the Medtronic SynchroMed® Infusion System. The SynchroMed pump is an implantable, programmable, battery-powered infusion device.

INDICATIONS

The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intraspinal infusion of preservative-free morphine sulfate sterile solution (10 mg/mL and 25 mg/mL) in the treatment of chronic intractable pain.

For the indications and instructions for use of Medtronic SynchroMed Models 8611H or 8615 Programmable Pumps, refer to the Medtronic SynchroMed Model 8610H/8611H/8615 technical manual.

CONTRAINDICATIONS

The device should not be implanted in the presence of infection.

Implantation is contraindicated when the pump cannot be implanted less than 2.5 cm (one inch) from the surface of the skin and/or when the patient has an implanted programmable medical device.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable candidates.

Contraindications relating to the use of the prescribed drug should be observed.

WARNINGS AND PRECAUTIONS

Reservoir filling must be performed by fully trained and qualified personnel, following the directions provided in the Medtronic SynchroMed Model 8551 Refill Kit Technical Instructions. Care should be taken in selecting the proper refill frequency to prevent depletion of the reservoir which would result in exacerbation of severe pain. To ensure adequate drug stability, refill intervals should not exceed 28 days. Strict aseptic technique is required while filling the reservoir to avoid bacterial contamination and infection. The SynchroMed refill kit must be used during all refills of the SynchroMed pump reservoir. **Extreme care must be taken to ensure that the needle is properly placed in the fill port of the device before attempting to refill the reservoir. Injecting the solution into the tissue around the device or attempting to inject the refill dose into the catheter access port will result in a large, clinically significant, overdosage to the patient.**

A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir. Before discharge, the patient and attendant(s) should receive instruction in the proper home care of the device and implant site, and in the recognition and practical treatment of an overdose of intraspinal morphine.

For a complete list of drug warnings and precautions for use, please refer to the appropriate sections of the drug labeling.

Refer to the appropriate Technical Manual for the SynchroMed Programmable Pumps for warnings, cautions and precautions.

POTENTIAL COMPLICATIONS

Clinical trials were performed to establish the safety and efficacy of the SynchroMed Infusion System. Based upon the data collected during these clinical trials, the potential complications associated with the use of the SynchroMed Infusion System may include, but may not be limited to: Cessation of therapy due to pump battery depletion or random component failure; pocket seroma, hematoma, erosion, or infection; catheter migration, angulation or dislodgement; lumbar puncture-type headache.

DOSAGE AND ADMINISTRATION

Refer to the package insert for preservative-free morphine sulfate sterile solution for dosage instructions for intraspinal infusion.

Pumps must be refilled on a prescribed schedule by trained personnel using procedures described in the SynchroMed Refill Kit Technical Manual.

The SynchroMed Refill Kit must be used during all refills of the SynchroMed pump reservoir.

Preservative-free morphine sulfate sterile solution is available commercially in single use ampules in the following concentrations:

200mg/20mL (10mg/mL)
500mg/20mL (25mg/mL)

These formulations are stable in the SynchroMed pump reservoir for 90 days. Refill intervals should not exceed 90 days.

The ability to noninvasively program the pump provides flexible control over both the dose and the timing of medication delivery. The programming feature allows dose adjustment or titration without changing the drug concentration in the reservoir.

Dilution is not necessary in most cases. Proper dosage may be selected by noninvasively adjusting the SynchroMed pump flow rate.

The minimum recommended pump flow rate is 0.096mL/day. Dilution is required for patients who require less than 1mg/day. Use a 0.9% solution of sodium chloride as a diluent.

See Table I for sample flow rates and refill intervals.

TABLE I

Sample Flow Rates and Refill Intervals

Patient Daily Dose (mg)	Morphine Concentration (mg/mL)	Recommended Flow Rate (mL/day)	Refill Interval (days) (a)
0.5	5(b)	0.1	90
1.0	10	0.1	90
2.5	10	0.25	64
2.5	25	0.1	90
5.0	10	0.5	32
5.0	25	0.2	80
7.5	25	0.3	53
10.0	25	0.4	40
20.0	25	0.8	20
25.0	25	1.0	16
30.0	25	1.2	13
40.0	25	1.6	10
50.0	25	2.0	8

(a) The refill interval considers the reservoir being filled with 18 mL, the low reservoir alarm set at 2 mL, and a drug stability in the pump reservoir of 90 days. Refill intervals should not exceed 90 days.

(b) Dilution is necessary. Use a 0.9% solution of preservative-free sodium chloride for diluent.

OVERDOSAGE

Overdosage of morphine is characterized by respiratory depression, with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center, or as the result of hypoxia, primary attention should be given to the establishment of adequate

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respiratory exchange through provision of a patent airway and institution of assisted, or controlled, ventilation. The narcotic antagonist naloxone is a specific antidote. An initial dose of 0.4 to 2 mg of naloxone should be administered intravenously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of narcotic-induced, or partial narcotic-induced, toxicity should be questioned. Intramuscular or subcutaneous administration may be used if the intravenous route is not available.

As the duration of effect of naloxone is considerably shorter than that of intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization.

TECHNICAL SUPPORT

A toll-free technical support service is available 24 hours a day for clinicians managing SynchroMed Infusion System implants: Telephone Customer Service at : 1-800-328-0810.

REFERENCES

1. SynchroMed Infusion System, Programmable Pumps Technical Manual.
2. SynchroMed Infusion System, System Description.
3. SynchroMed Infusion System, Intraspinal Catheter Technical Manual.
4. SynchroMed Infusion System, Refill Kit Technical Instructions.

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